CLINICAL REVIEW

for advisory committee background package

Application Type	NDA
Submission Number	21-887
Submission Code	000
Letter Date	June 6, 2005
Stamp Date	June 7, 2005
PDUFA Goal Date	April 7, 2006
Reviewer Name	Karen B. Feibus, M.D.
Review Completion Date	December 1, 2005
Established Name	orlistat
(Proposed) Trade Name	Alli
Therapeutic Class	pancreatic lipase inhibitor
Applicant	GlaxoSmithKline Consumer Healthcare
Priority Designation	S
Formulation	60 mg capsules
Dosing Regimen	1 – 2 capsules up to TID with fat containing meals
Indication	weight loss
Intended Population	overweight adults ages 18 years and older

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Pending advisory committee meeting

1.2 Recommendation on Postmarketing Actions

Pending advisory committee meeting.

1.3 Summary of Clinical Findings

GlaxoSmithKline Consumer Healthcare, L.P. (GSKHC), submitted NDA 21-887 for orlistat 60 mg capsules to promote weight loss in overweight adults, age 18 years and older, when used along with a reduced calorie, low-fat diet. The proposed trade name is *Alli*. The proposed dosing regimen is 1 – 2 capsules (60 – 120 mg) with each fat-containing meal, up to three times per day (TID) with a labeled six-month duration of use. Orlistat, tetrahydrolipistatin, is a reversible pancreatic lipase inhibitor that acts by inhibiting the absorption of approximately 30% of dietary fat.

1.3.1 Brief Overview of Clinical Program

GSKHC submitted data from seven studies to support the safety and efficacy of orlistat OTC 60 mg as an OTC weight loss product. The safety and efficacy of orlistat 120 mg for the treatment of obesity and weight management was reviewed and approved in NDA 20-766 in April 1999. Four of the currently submitted trials were submitted to NDA 20-766 but also contained 60 mg orlistat treatment arms. Three additional studies, including the actual use study reviewed in this document, were submitted in their entirety to NDA 21-887. Brief descriptions of these studies are provided in the table below:

Table A: Studies submitted to NDA 21-887 for orlistat OTC, 60 mg

Study No./Completion Date/NDA #	Type of study	Role in OTC NDA	Duration of study	BMI (kg/m^2)	Orlistat treatment	Number of subjects
NM14161 February 1995 N20-766	Weight loss study using primary care providers	Safety and efficacy	2 yrs	30 – 43	Placebo 60 mg 120 mg	212 213 210
BM14150 May 1995 N20-766	Dose-ranging study	Safety and efficacy	6 mths	28 – 43	Placebo 30 mg 60 mg 120 mg 240 mg	124 122 123 120 117

Table A: Studies submitted to NDA 21-887 for orlistat OTC, 60 mg						
Study No./Completion Date/NDA #	**Type of study**	**Role in OTC NDA**	**Duration of study**	**BMI (kg/m^2)**	**Orlistat treatment**	**Number of subjects**
BM14149 February 1996 N20-766	Weight loss study	Safety and efficacy	2 yrs	28 – 43	Placebo 60 mg 120 mg	237 239 242
NM14302 March 1996 N20-766	Weight maintenance effect of orlistat after 6 month period of weight loss with diet alone	Safety	18 mths*	28 – 38	Placebo 30 mg 60 mg 120 mg	185 186 171 180
RCH-ORL-002 December 2001 N21-887	Evaluation of orlistat treatment in a "naturalistic setting"	Safety	4 wks	**	60 mg	162
NM17247 October 2003 N21-887	Weight loss study in a primary care setting	Safety and efficacy	4 mths	25 – 28	Placebo 60 mg	195 196
NM17285 October 2003 N21-887	Pilot actual use study	Actual use and safety	3 mths	**	60 – 120 mg	284

*12 months of drug treatment
** These studies were intended to simulate an OTC environment; no BMI restrictions imposed.

A label development section and pivotal label comprehension study were also submitted to this NDA. These portions of the submission are reviewed by Arlene Solbeck, M.S., interdisciplinary scientist, and Susanna Weiss, Ph.D., behavioral scientist in separate review documents. The orlistat OTC starter pack includes six supplementary support materials: a companion guide (user's guide), QuickFacts cards, a Healthy Eating Guide, a Daily Journal, a Calorie and Fat Counter, and a Welcome Card that introduces the consumer to the behavioral support program. These materials are included as an integral part of the Alli Weight Loss Program. These educational support materials, while based on those used in the actual use study, were designed by the sponsor after completion of the actual use study by Roche, Inc.

The integrated summaries of efficacy and safety submitted by the sponsor are reviewed by Dr. Julie Golden from the Division of Metabolism and Endocrinologic Products. This document reviews study NM17285, the pilot actual use study. Comments that follow relate to findings from this study unless otherwise specified.

1.3.2 Efficacy

The efficacy of orlistat OTC for weight loss when used in an actual use setting is reviewed in this document based on data from study NM17285. This study was conducted by the drug innovator, Roche, Inc.

The primary objectives of the actual use study were to:

- evaluate the ability of consumers to correctly select or de-select orlistat for personal use based on labeled directions

- provide initial information regarding how consumers use and dose orlistat without physician supervision
- evaluate the adverse event profile in an actual use setting.

Subject weight loss was not a pre-specified study endpoint. The sponsor's secondary objectives were to assess consumer perceptions of orlistat and evaluate the consumer educational materials and website. The consumer educational materials included the following:

1. **How to Lose Weight with Orlistat**
   A 12-page booklet containing information about: how to correctly use and dose orlistat, possible side effects; who should not use orlistat; when to stop using orlistat. The booklet encouraged eating three balanced meals a day, counting calories and fat grams, and provided some instruction in reading a ***Nutritional Facts*** label. The booklet addressed "common dieting pitfalls."

2. **Orlistat Food Diary: Keep track of your progress**
   Subjects were instructed to record foods eaten, physical activity, and to check the orlistat box when they took an orlistat dose.

3. **Fat Counter**
   Pocket-size Harriet Roth's Fat Counter which contained more than 70 pages of information on fat grams and calories for many food items with brand name comparisons.

4. **Fat Wheel**
   A cardboard wheel that provided fat grams and portion sizes for common foods (yogurt, eggs, soups and sauces, cheese, beef, veal and lamb, pork, chicken and turkey, fish and shellfish, beans and peas, vegetables, fruits, breads, pasta and grains, breakfast foods, spreads and dressings, snacks, beverages, frozen sweets, and sweets).

5. **Portion Card**
   A two-sided laminated card with tips about portion and serving sizes.

6. **Diet Success Planner**
   A 27-page booklet divided into five sections that included information on setting eating and activity goals, planning meals and food shopping lists, calories and food, healthy cooking and snack suggestions, food exchanges and sample menus, exercise, and dining out.

This three month, pilot actual use trial was a multi-center, pharmacy-based, open-label, three-month trial. Eighteen pharmacies, in six geographical areas of the United States participated in the study. Each pharmacy was equipped with a certified, calibrated scale. In-store advertising was the primary recruitment method. During the study, recruitment numbers were too low at seven pharmacy sites. In these areas, advertisements were placed in local newspapers to accelerate recruitment at these sites.

Eligible subjects were 18 years of age and older and able to participate in telephone follow-up interviews. Individuals who had previously used orlistat were excluded. Recruited individuals were allowed to participate in the self-selection decision but were not allowed to purchase if they were allergic to orlistat, pregnant or breastfeeding, or currently treated with cyclosporine, warfarin, or a medicine for diabetes.

The pharmacy staff followed a script, and all potential subjects were asked to review the label for the proposed product (see section 10.4). The following self-selection question was asked:

> *Do you think this medication is appropriate for you to use?*

Demographic information, medical history, and an objective weight measurement were collected at the time of enrollment. Informed consent was obtained. The REALM test was administered. The purchase decision question was then asked:

> *The cost of this mediation is $45 for a bottle of 90 capsules. Would you like to purchase this medication today?*

Responses and reasons were recorded. Purchasers were allowed to purchase up to three bottles of study drug at a time but were allowed to return to the pharmacy as often as desired to purchase more medication. Subjects who did not purchase orlistat at the time of enrollment were not allowed to return at a later time to purchase orlistat. Follow-up pharmacy visits were not scheduled or required, even at the end of the study. Therefore, there were no required objective weight measurements following the weigh-in at enrollment. Four follow-up telephone interviews were scheduled at pre-set intervals of 14, 30, 60, and 90 days plus an end of study telephone interview two weeks after cessation of study drug treatment. Interview timing was allowed to vary within a ten day window. Telephone interviews used a computer-assisted (CATI) program to prompt questions sequentially based on answers entered. Answers were often multiple choice or *best choice* answers chosen by the clinical interviewers. Verbatim answers were recorded only with regard to some defecation pattern adverse event reports.

Study results

A total of 703 individuals was screened . Ultimately, 681 subjects were eligible for study participation (after 22 subjects from one pharmacy site were later excluded due to protocol violations) and participated in the self-selection decision. Of 681 eligible subjects, 79.7% thought that orlistat was appropriate for them to use, 7.6% thought it was not appropriate for them to use, and 12.6% did not know or were unsure. Overall, eligible subjects had a total of 839 labeled contraindications to use. Correct self-selection decisions were made for 28% of these labeled contraindications. If incorrect self-selection decisions based on the labeled contraindication *more than 30 pounds to lose* are excluded, then correct self-selection decisions were made for 62% of labeled contraindications. Table B shows the number and percentage of incorrect self-selection and use decisions for each labeled contraindication.

Table B: Summary of self-selection and use decisions among actual use study subjects with one or more labeled exclusions (N = 465)			
Actual Use Study Label Exclusion criterion (U = unconditional) (C = conditional)	**Subjects with labeled exclusion(s)** (N = 465)	**Appropriate self-selection decision**	**Appropriate use decision**
Allergic to ingredients (U)	0	N/A	N/A
Taking cyclosporine (U)	2 (0.3%)	50.0%	N/A
Taking warfarin (U)	14 (2.1%)	50.0%	N/A
Taking diabetes medicine (U) †	46 (6.8%)	34.8%	N/A
Problems absorbing food (C)	12 (1.8%)	16.7%	0% (0 of 1)
Gallbladder problems (C)	25 (3.7%)	40.0%	28.6% (2 of 7)
High blood pressure (C)	166 (24.4%)	44.0%	38.9% (21 of 54)
High cholesterol/triglycerides (C)	147 (21.6%)	46.3%	42.9% (21 of 49)
More than 30 pounds to lose (C)	346 (50.8%)	21.1%	23.7% (27 of 114)
On diet recommended by doctor (C)	48 (7.0%)	54.2%	50.0% (5 of 10)
Taking another weight loss medicine (C)	33 (4.8%)	12.1%	25.0% (3 of 12)

By labeled contraindication, appropriate use decisions were made by subjects 0 – 50% of the time depending on the particular labeled contraindication.

Reviewer comment:

1. *It is not clear whether consumers understand the meaning of "problems absorbing food."*

Subjects used orlistat for a mean of 67 days with a range of 3 – 90 days of use. Nearly all users used an appropriate daily dose of orlistat and took the appropriate number of capsules per dose. Ongoing use of orlistat declined throughout the study. Only 46.4% of orlistat users were still using study drug at the Day 90 telephone interview.

Concomitant use of a multivitamin containing fat-soluble vitamins is recommended with orlistat use due to documented decreased absorption of vitamins D, E, and beta-carotene and potential for decreased absorption of vitamins A and K. As stated in the medical officer review of orlistat safety for NDA 20-766 (by Eric Coleman, M.D.), long term orlistat treatment does not appear to cause frank vitamin K deficiency as assessed with prothrombin time. However, prothrombin time is not a sensitive indicator of vitamin K deficiency and may remain normal with mild to moderate vitamin K deficiencies. Published literature suggests that fat malabsorption is

associated with vitamin K deficiency.[2] In controlled, clinical trials, plasma retinol levels did not differ significantly between 120 mg orlistat and placebo treatment groups following two years of treatment; however, while not significantly different, the incidence of low plasma retinol levels in the orlistat group were twice that in the placebo group. Based on data from the 174 subjects who completed the 14 day telephone interview, twenty-four percent of orlistat users took a multivitamin (MVI) regularly; however only 54% of these subjects took the MVI at least two hours before or after orlistat as instructed by the label. The sponsor did not provide MVI use information beyond the 14 day telephone interview.

Seventy-seven to 86% of subjects found the supplemental educational materials helpful. At the beginning of the study, about 80% of subjects were following some kind of diet, but this percentage declined to 61% by the end of the study. Most study subjects used a reduced calorie and/or low-fat diet. Seventy-three percent of subjects perceived that orlistat *was helpful in helping them lose weight*.

Based on self-reported weights, the mean weight loss during the three month study period was 4.8 kg. The mean measured weight loss at the end of study participation was 3.3 kg based on objectively measured weights at the pharmacy in 106 of 237 (44.7%) users who returned to the pharmacy for a last visit as requested. Based on measured weights taken at study day 60 and beyond, 42% of subjects lost more than 5% of their body weight; however, this figure is based on weights from only 25% of the user population. Based on self-report at the final telephone interview, 41% of all study subjects using orlistat lost more than 5% of their body weight. For comparison, obese subjects who enrolled in randomized, placebo-controlled studies and used orlistat 60 mg and 120 mg lost an average of 4.26 kg and 4.65 kg respectively with six months of treatment; however, weight loss above and beyond that of the placebo group averaged 2.4 – 2.8 kg. Weights during the randomized, controlled trials were objectively measured by study personnel. In general, individuals with higher baseline body mass indexes (BMI) lost more weight than those with lower baseline BMIs both in controlled clinical trials and in the actual use study.

It appears that the majority of subjects enrolled in the actual use study complied with dosing instructions and lost weight using orlistat and the accompanying behavior support program. The adverse event profile among actual use study subjects closely parallels the adverse event profile seen among prescription users of orlistat, and no new safety signals were detected. Correct multivitamin use among study subjects was inadequate even though it increased from 38% to 54% over the course of the study. The low rates of correct self-selection and use decisions among subjects with labeled exclusions is concerning. Based on LC study results that suggest >85% comprehension on most label warning elements, this poor performance may be based on consumer non-compliance rather than lack of comprehension.

Study results are confounded by incomplete or inadequate objective and prospective data collection. Some reimbursement procedures during the study and certain questions during the telephone interview may have influenced subject behavior during the study. These study design and data deficiencies make it impossible to convincingly document consumer orlistat use behaviors and weight loss benefit.

1.3.3 Safety

This summary of safety data will focus on two areas: safety issues related to self-selection and use decisions and adverse events experienced by subjects during the study.

Subject self-selection decisions suggest either a problem with label comprehension or extensive disregard for label warnings. As shown in Table B above, the majority of subjects with a labeled contraindication thought that orlistat was appropriate for them to use. Even when self-selection and use decisions are examined for only the labeled exclusions that remain on the proposed NDA label, correct self-selection and use decisions by subjects ranged between 0 – 50% for unconditional exclusions and 12.1 – 50.0% for conditional exclusions. The sponsor did not provide data to confirm whether subjects with conditional exclusions consulted their healthcare professional as claimed, so incorrect behavioral decisions rates could be higher.

This actual use study did not test consumer behaviors on label elements new to the NDA label. The submitted NDA label contains the following new label communications:

- a new conditional exclusion for consumers with kidney stones
- a new unconditional exclusion for consumers who are not overweight
- a change in labeling from conditional to unconditional exclusions for consumers who are pregnant or breastfeeding and consumers who have problems absorbing food.

Consumer behaviors related to these label elements were not evaluated by this study (see section 10.5). Study population demographics show that 7.5% of orlistat users in the actual use study were not overweight.

Orlistat use decreases the absorption of fat soluble vitamins A, D, E, and K and beta-carotene from the intestines. Consistent with current prescription labeling, the proposed OTC label recommends that consumers take a daily multivitamin (MVI) while using orlistat. To ensure absorption of the vitamin supplements, the label instructs consumers to take the MVI at least two hours before of after orlistat. The sponsor only reported MVI use at the first telephone interview, which occurred at about study day 14. At that time, 74% of orlistat users reported taking a MVI at least a few times per week, but only 54% of these subjects timed the MVI correctly with their orlistat dosing (40% of the orlistat users). The reason for this noncompliance is unclear. The communication on the orlistat label may not be clear to consumers or consumers may be confused by conflicting instructions for use on the MVI label. The orlistat labeling does not inform consumers that instructions on the MVI label may be different in relation to timing with food. It is possible that consumers may use repeated courses of orlistat OTC over time and may choose to continue orlistat use beyond its labeled duration of use to maintain or continue weight loss. This combined with the long-term risk of vitamin deficiency without effective vitamin supplementation is a concern. This study does not offer insight into these potential behaviors because the study did not continue beyond a 90-day drug treatment period. Subject compliance with label communications that address duration of use were not evaluated.

No deaths occurred in the actual use study. There were six serious adverse events that occurred in five subjects: one kidney infection, one methicillin-resistant staphylococcus aureus urinary tract infection (MRSA UTI), one abdominal pain, one chest pain, one spontaneous abortion, and one transient ischemic attack (same subject as MRSA UTI). The episode of abdominal pain in a 46-year old anemic female and the episode of chest pain in a 48 year old female were considered possibly related to study drug. The subject with abdominal pain had a normal diagnostic work-up in the emergency department except for a low hematocrit. She had an eight year history of anemia and refused a blood transfusion. The subject with chest pain was diagnosed with esophageal spasm and two subsequent episodes of similar pain were successfully treated with hyoscyamine. The pregnancy loss occurred at 22 – 26 weeks gestation following orlistat use from 8 – 11 weeks gestation. A pregnancy loss is not considered a spontaneous abortion if it occurs after 20 weeks gestation. Medical records were not released by the subject.

Based on orlistat's mechanism of action, defecation pattern adverse events are expected due to the passage of more fat in the stool. Defecation pattern adverse events included:

- oily spotting
- fecal urgency
- liquid stools
- fecal incontinence
- fatty/oily stool
- flatus with discharge
- increased defecation
- decreased defecation
- soft stools
- oily evacuation

Approximately 50% of subjects experienced a defecation pattern adverse event at some time during the study. The incidence was the same regardless of whether subjects used 60 mg or 120 mg of orlistat per dose. Sixty-five to 90% of subjects experiencing various defecation pattern adverse events continued orlistat use without interruption. The remainder of these subjects either interrupted or discontinued orlistat use due to these adverse events. A total of 43 subjects (15.8% user population) discontinued orlistat treatment due to adverse events, and 21 of these cases were defecation pattern adverse events. The other adverse events leading to discontinuation in the other 12 subjects were: viral gastroenteritis, upper respiratory tract infections, chest pain, fatigue, hypertension, back injury, abnormal cardiovascular function test, carpal tunnel syndrome, and periorbital edema. The following adverse events were considered treatment-related: upper abdominal pain (3.5%), fatigue (2.5%), headache (2.1%), dyspepsia (1.8%), muscle cramps (1.4%), hemorrhoids (1.4%), chest pain (1.1%), constipation (1.1%), vomiting (0.7%), and frequent bowel movements (0.7%). The overall adverse event profile among actual use study subjects was very similar to the adverse event profile of subjects taking orlistat 60 mg of 120 mg in randomized, controlled clinical trials.

The adverse event profile seen among actual use study subjects does not raise safety concerns for consumer use. However, the frequency of incorrect self-selection and use decisions by subjects with labeled contraindications and incorrect MVI supplementation are unresolved consumer safety concerns. Consumer behavior in an actual use study on orlistat use has not been done using the actual label and supplemental educational materials submitted with this NDA.

1.3.4 Dosing Regimen and Administration

The sponsor proposes a dosing regimen for orlistat 60 mg capsules of one to two capsules with fat-containing meals up to three times per day. Labeling recommends starting with the lower dose. Orlistat must be taken with meals in order to inhibit fat digestion and absorption. The prescription dose for orlistat is 120 mg up to TID. The safety profile of orlistat is very similar at the 60 mg and 120 mg doses. The dosing regimen proposed is reasonable and supported by dose-ranging studies submitted to NDA 20-766.

1.3.5 Drug-Drug Interactions

Orlistat treatment produces a documented decrease in the absorption of vitamins D, E, and beta-carotene and a potential for decreased absorption of vitamins A and K. Use of orlistat within two hours of cyclosporine dosing reduces serum levels of cyclosporine. Drug-drug interaction studies have shown that orlistat has no effect on the pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended release tablets), oral contraceptives, phenytoin, pravastatin, warfarin, or metformin.[5]

1.3.6 Special Populations

Not applicable.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

On June 6, 2005, GlaxoSmithKline (GSK) Consumer Healthcare, L.P., submitted NDA 21-887 for orlistat 60 mg capsules to promote weight loss in overweight adults, age 18 years and older, when used along with a reduced calorie, low-fat diet. The proposed trade name is *Alli*. The proposed dosing regimen is 1 – 2 capsules (60 – 120 mg) with each fat-containing meal, up to three times per day (TID). Orlistat, tetrahydrolipistatin, is a pancreatic lipase inhibitor that acts by inhibiting the absorption of approximately 30% of dietary fat. Three percent of the drug is systemically absorbed, and most of the absorbed drug is rapidly metabolized to pharmacologically inactive compounds during first pass through the entero-hepatic circulation.

Hoffmann-La Roche, Inc. first submitted an investigational new drug application (IND 31,617) for orlistat capsules on May 13, 1988. On April 23, 1999, NDA 20-766 was approved for the prescription-only marketing of Xenical®, orlistat 120 mg TID. A pediatric indication for children down to the age of 12 years was approved by FDA on June 12, 2004. Xenical use is indicated for obese patients with an initial body mass index (BMI) $\geq$ 30 kg/m^2 or $\geq$27 kg/m^2 in the presence of other risk factors (hypertension, diabetes, dyslipidemia). The product should be used in conjunction with a reduced calorie diet, and indications for use include: obesity management, weight loss, and weight maintenance.

On June 19, 2001, FDA received a Hoffmann-La Roche, Inc. application for IND 62,758 to investigate the development of orlistat for OTC marketing. In September 2004, GSK acquired ownership of IND 62,758 from Hoffmann-La Roche, Inc. GSK has right of reference to relevant information within IND 31,617 and NDA 20-766, but the ownership of and responsibility for this application remains with Roche. Some of the pivotal Xenical® studies conducted under IND 31,617 included 120 mg and 60 mg orlistat treatment groups.

2.2 Currently Available Treatment for Indications

FDA-approved weight loss and obesity management drug products are regulated though NDAs for prescription products. Drugs marketed prescription-only for obesity management include appetite suppressants and orlistat. There is an over-the-counter (OTC) drug monograph for weight control products, but it is not yet finalized.

Phentermine hydrochloride (HCl)
Phentermine HCl is a sympathomimetic amine with amphetamine-like pharmacologic activities such as appetite suppression (anorexia). The primary action of this drug in treating obesity may be a central nervous system (CNS) or metabolic effect other than appetite suppression. Adult obese patients using dietary management lose more weight when treated with phentermine as

opposed to placebo. The weekly difference in weight loss between treatment groups is a fraction of a pound per week and results are inconsistent from study to study. In a weight reduction program based on exercise, behavioral modification, and caloric restriction, physicians may use phentermine as a short-term (a few weeks) adjunct to obesity management in patients with a body-mass index (BMI) $\geq$ 30 kg/m^2 or with a BMI $\geq$ 27 kg/m^2 and other co-existing risk factors (hypertension, diabetes, hyperlipidemia). Phentermine compounds are taken as an oral tablet or capsule.

Phentermine use is contraindicated in individuals with arteriosclerosis, cardiovascular disease, moderate to severe hypertension, hyperthyroidism, glaucoma, and known hypersensitivity or idiosyncrasy to the sympathomimetic amines. Primary pulmonary hypertension (PPH) has occurred in patients receiving a combination of phentermine with fenfluramine or dexfenfluramine. There have been rare cases of PPH in patients who took phentermine alone. Phentermine is approved as a monotherapy for obesity management and should not be combined use with other drug products for weight loss.

Phentermine has the potential for abuse given its chemical and pharmacological relationship to amphetamine. Abuse of these types of drugs may be associated with psychological dependence and social dysfunction. Sudden cessation of use may lead to withdrawal symptoms including extreme fatigue and mental depression.[1, 3]

Methamphetamine hydrochloride
Methamphetamine HCl is a sympathomimetic amine with CNS stimulant activity. Peripheral pharmacologic actions include elevation of systolic and diastolic blood pressure and weak bronchodilation and respiratory stimulation. The mechanism of action and magnitude of weight loss effect are the same as that defined above for phentermine. While methamphetamine is indicated for the treatment of obesity in conjunction with a weight reduction program in patients refractory to other therapies, the drug carries a black box warning due to its high potential for abuse and drug dependence. Contraindications are the same as those listed for phentermine and also include use of a monoamine oxidase inhibitor within 14 days.[1, 3]

Sibutramine hydrochloride monohydrate
Sibutramine HCl monohydrate is a norepinephrine (NE), serotonin, and dopamine reuptake inhibitor. The parent compound is metabolized to two active amines, M1 and M2. M1 and M2 both inhibit NE, serotonin, and dopamine reuptake in vivo in the human brain. Sibutramine is indicated for the management of obesity, including weight loss and weight loss maintenance, in conjunction with a reduced calorie diet. It is recommended for use in individuals with a BMI $\geq$ 30 kg/m^2 or with a BMI $\geq$ 27 kg/m^2 in the presence of other risk factors (hypertension, diabetes, hyperlipidemia). Use of sibutramine is contraindicated in patients:

- on a MAOI
- with uncontrolled or poorly controlled hypertension
- with cardiovascular disease, congestive heart failure, arrhythmias, or stroke
- with an eating disorder
- taking other centrally acting appetite suppressants

- with hypersensitivity to the drug or the inactive ingredients.

Regular blood pressure monitoring is required during use, as sibutramine use substantially increases blood pressure. No cases of pulmonary hypertension have been reported associated with sibutramine use. [1, 3]

Weight Control Products and OTC Marketing
FDA recognizes weight control as an OTC indication and weight control products have been marketed over-the-counter. The Advanced Notice of Proposed Rulemaking (ANPR) for Weight Control Products for Over-the-Counter Human Use was published on February 26, 1982. As recommended by the National Academy of Sciences Advisory Review Panel, two appetite suppressants were classified as Class I ingredients (GRAS/GRAE):

1. Phenylpropanolamine (PPA)
2. Benzocaine

In 2000, PPA was voluntarily removed from OTC drug products due to an increased risk of hemorrhagic stroke associated with use, and a final rule reclassifying PPA as a category II monograph ingredient is pending. A final rulemaking is in progress or benzocaine, which is currently Category III for efficacy for weight control.

The ANPR required inclusion of the following labeling for OTC weight control products:

1. "This product's effectiveness is directly related to the degree to which you reduce your usual daily food intake. Attempts at weight reduction which involve the use of this product should be limited to periods not exceeding 3 months, because that should be enough time to establish new eating habits."

2. Indication for use:
   "for appetite control to aid weight reduction"
   "an aid for effective appetite control to assist weight reduction"
   "helps curb appetite"
   "appetite depressant in the treatment of obesity"
   "an aid to diet control in conjunction with a physician's recommended diet"
   "an aid in the control of appetite"
   "helps control appetite"
   "for use as an aid to diet control"
   "helps you eat less, weigh less."

At this time, there is no Final Rule.

2.3 Availability of Proposed Active Ingredient in the United States

On April 23, 1999, FDA approved NDA 20-766, orlistat 120 mg (tetrahydrolipistatin) for the long-term treatment of obesity in patients (ages 17 years and above) with a body mass index (BMI) $\geq$ 30 kg/m^2 or a BMI $\geq$ 27 kg/m^2 and other risk factors such as hypertension, diabetes, and dyslipidemia. Orlistat should be used in conjunction with exercise and a reduced calorie, low-fat diet for weight loss, maintenance of weight loss, and prevention of weight regain.

On March 19, 2001, Hoffman – La Roche Inc. submitted a NDA supplement for the indication of *combination therapy for improvement in glycemic control in type 2 diabetics who are overweight or obese*. While statistical analyses suggested a possible modest benefit for the combined use of orlistat with a sulfonylurea or with insulin, this benefit was not seen with metformin combination therapy and the decreases in hemoglobin A_1C levels were inconsistent and modest. (1/17/2002, DMEP medical officer review by Joanna K. Zawadzki, M.D.) The additional proposed orlistat indication for type 2 diabetes treatment was not approved.

FDA approved a NDA supplement for the use of orlistat in the management of obesity in adolescent patients ages 12 years and above on December 12, 2003.

2.4 Important Issues With Pharmacologically Related Products

Orlistat is the only member of this pharmacological class of drugs.

2.5 Presubmission Regulatory Activity

On July 17, 2002, prior to GSKHC's acquisition of IND 62,758, Hoffmann-La Roche met with FDA for an end of phase II meeting. As conveyed by the meeting minutes, FDA identified key issues requiring further assessment for OTC orlistat development. GlaxoSmithKline Consumer Healthcare, L.P. addressed these issues in their November 4, 2004, pre-NDA submission. The following issues were discussed by GSK, the Division of Metabolic and Endocrine Products, and the Office of Nonprescription Products at the December 8, 2004 pre-NDA meeting.

2.5.1 Justification for the selection of a 60 mg dose for OTC use and for keeping the 120 mg dose prescription only

In NDA 21-887, the proposed indication for orlistat 60 mg is *promote weight loss in overweight adults when used along with a reduced calorie and low fat diet*. The dose is one to two capsules with each meal containing fat, not to exceed six capsules per day.

2.5.2 Lack of data supporting the safety and effectiveness of orlistat in patients without dietary or exercise counseling

The sponsor submitted results from this pilot actual use study (NM 17285) and study NM 17247 to support the safety and efficacy of orlistat in patients/consumers without dietary or exercise counseling. Study NM 17247 was a six-month, randomized, placebo-controlled, parallel design study in patients with BMI 25 - <28 kg/m^2 in a primary care setting.

2.5.3 Number of allowable OTC treatment courses before a consumer should consult a healthcare provider for alternative approaches to weight loss

Labeling submitted with the current NDA as supplemental educational materials suggests that consumers may repeat the six-month course of OTC orlistat therapy if they have not taken the drug in three months. This information does not appear in the Drug Facts label, and there is no recommendation to speak to a healthcare provider prior to repeating OTC courses of orlistat.

2.5.4 Need for an actual use study to address the following issues:

Does it matter whether both overweight and obese consumers use OTC orlistat?
Do consumers stop using OTC orlistat after six months?
How likely are consumers to use a MVI concomitantly with OTC orlistat treatment?

The pilot actual use study (NM 17285) was a four month study with 90 days of treatment, and the proposed duration of use for OTC orlistat is six months. The sponsor was informed that in order to gather consumer behavioral information on appropriately-timed drug discontinuation, FDA prefers to see an actual use study that lasts longer than the product's labeled duration of use. The sponsor was asked to demonstrate how data from the pilot actual use study could be meaningfully extrapolated to predict consumer behavior at six months.

Based on the pre-NDA meeting package materials and discussion at the pre-NDA meeting, the Agency made the following recommendations regarding the anticipated NDA submission for OTC orlistat:

1. The standards used to evaluate and label effectiveness of OTC weight loss products should be the same as those for prescription weight loss products. As outlined in the 1996 draft guidance, these standards include meeting one of the following two criteria:

   - Demonstration that the drug effect is significantly greater than the placebo effect, and the mean associated weight loss exceeds the mean placebo weight loss by at least 5%.

- Demonstration that the proportion of subjects who reach and maintain a weight loss of at least 5% of their initial body weight is significantly greater in subjects on study drug than on placebo.

- This weight loss should be maintained over 12 months. There is no specific time allowed for weight loss to occur.

2. Based on existing safety and efficacy data, the orlistat dose for OTC marketing can be 60 – 120 mg TID. FDA noted that previously submitted data demonstrate a 3% weight loss overall for subjects treated with orlistat 60 mg TID among previously conducted studies of 4 – 24 months duration. The 3% body weight loss does not meet the weight loss criteria contained in the draft guidance cited above. There are no clear safety concerns to prohibit the 120 mg orlistat dose from going OTC.

3. The sponsor should demonstrate that effective dietary and exercise guidance can be provided in the OTC setting so that consumers optimize and maintain their weight loss. The sponsor should consider conducting a longer (12 month) actual use study that compares active treatment to placebo and enrolls a low literacy population.

4. Any label comprehension studies should be submitted with the NDA for review by the Division of OTC Drug Products.

5. Pediatric studies should be conducted down to at least age 12 years. This population is likely to use this product whether or not individuals meet the criteria for *overweight* or *obese*. The 120 mg dose is approved as a prescription drug in this age group.

6. The sponsor needs to address any safety issues regarding chronic vitamin malabsorption. Co-packaging a multivitamin with 60 mg orlistat should be considered.

7. The potential for misuse among non-overweight individuals, especially those with eating disorders, will need to be addressed.

2.6 Other Relevant Background Information

In 1996, the Division of Metabolic and Endocrine Drug Products developed and issued a draft Guidance for Industry on the Clinical Evaluation of Weight-Control Drugs. This document suggests clinical trial and clinical drug development programs that could demonstrate the safety and efficacy of drugs to reduce body fat and thereby *improve health and self-esteem*. A final Guidance has not been issued, and the draft document is not available to industry.

The Guidance states that efficacy trials for proposed weight loss drug products should be randomized, double-blind, and placebo-controlled for at least the first 12 months of the clinical trial. Data collection under either open-label or blinded conditions should continue for 24 months. All participating study subjects should be instructed in diet, exercise, behavior modification, and other relevant lifestyle changes. Subjects should be moderately to markedly

obese with a BMI ≥ 30 kg/m2 or ≥ 27 kg/m2 for those with co-morbid conditions. Utilization of methods to measure percent body fat and body fat distribution is encouraged. The study population should include minorities and members of both sexes in numbers large enough to allow statistical evaluation under stratified conditions for these sub-groups.

Study subjects should be given a calorie-restricted or controlled diet, behavior modification, and exercise education. In order to identify placebo responders, all subjects should utilize these techniques during an initial six week period. Individuals who do not lose weight or individuals who plateau are randomized to study treatment or placebo.

Results should include actual weight loss and weight loss expressed as percent of body weight or percent of excess over ideal body weight (or BMI).

While the Guidance does not intend for the recommendations to apply to all possible weight-loss drug product evaluations, the following two weight-loss demonstrations are presented as viable primary efficacy outcome variables:

- Demonstration that the mean drug-associated weight loss exceeds the mean placebo-associated weight loss by at least five percent.

- Demonstration that the proportion of subjects who reach and maintain a weight loss ≥ 5% of initial body weight is significantly greater in subjects on the proposed drug than in those on placebo.

Reviewer Comment:

- *At the pre-NDA meeting (12/08/2004), the Division of Metabolic and Endocrine Products stated that the standards used to evaluate and label effectiveness of OTC weight loss products should be the same as those used for prescription weight loss products.*

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

The safety and efficacy reviews for orlistat 60 mg, NDA 21-887, were completed by Julie Golden, M.D. from the Division of Metabolic and Endocrine Products and can be found in the Division Files System (DFS).

3.1 CMC (and Product Microbiology, if Applicable)

Martin Haber, PhD, from the Division of Chemistry reviewed the CMC data, and his review can be found in DFS.

3.2 Animal Pharmacology/Toxicology

The sponsor references the nonclinical pharmacology and toxicology data from NDA 20-766 and has not submitted any new data. Fred Alavi, pharmacologist, completed the PharmTox review, and his review can be found in DFS.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is limited to the Actual Use study (NM17285) submitted with this NDA. Submitted labeling for the proposed product is compared to the labeling used in the Actual Use study. Submitted efficacy and safety data from other orlistat clinical trials are reviewed by Julie Golden, M.D., from the Division of Metabolism and Endocrinologic Products. The label comprehension study is reviewed by Susanna Weiss, Ph.D.

This review uses data from pivotal efficacy and safety studies submitted to NDA 20-766 to compare weight loss and adverse event profiles of subjects in the actual use study to the weight loss and adverse events experienced by subjects in randomized, placebo-controlled trials who received dietary counseling from a learned intermediary.

4.2 Tables of Clinical Studies

The following table lists the clinical studies included in NDA 21-887 for orlistat OTC. The sponsor also submitted complete individual study reports for 66 competed clinical pharmacology studies in 1438 patients

Table 1:
Listing of Studies to be included in OTC NDA for orlistat

Study No. / Study Completion Date	Type of Study	Role in OTC NDA	Duration	BMI	Dose
BM14149 February 1996	Weight loss study	Safety & Efficacy	2 yrs	28-43	Placebo 60 mg 120 mg
NM14161 February 1995	Weight loss study using primary care providers	Safety & Efficacy	2 yrs	30-43	Placebo 60 mg 120 mg
NM17247 October 2003	Weight loss study in a primary care setting	Safety & Efficacy	4 mos	25-28	Placebo 60 mg
BM14150 May 1995	Dose-ranging study	Safety & Efficacy	6 mos	28-43	Placebo 30 mg 60 mg 120 mg 240 mg
NM14302 March 1996	Weight maintenance effect of orlistat after 6 month period of weight loss by diet alone	Safety	18 mos*	28-38	Placebo 30 mg 60 mg 120 mg
RCH-ORL-002 December 2001	Evaluation of orlistat in a naturalistic setting	Supportive	4 wks	**	60 mg
NM17285 October 2003	Pilot actual use study	Supportive	3 mos	**	60 mg

*12 months of drug treatment
** These studies were intended to simulate an OTC environment; no BMI restrictions were imposed.

4.3 Review Strategy

Reviewers of NDA 21-887 are as follows:

- Efficacy and safety: Julie Golden, M.D., medical officer, Division of Metabolism and Endocrinologic Products
- Statistics: Joy Mele, statistician, Division of Metabolism and Endocrinologic Products
- Pharmacology/Toxicology: Fred Alavi, pharmacologist, Office of New Drugs
- CMC: Martin Haber, chemist, Division of Pre-marketing Assessment I

- Biopharmacology: Hae Young Ahn, pharmacologist, Division of Clinical Pharmacology and Biopharmaceutics 2

- Actual use study: Karen Feibus, M.D., medical officer, Division of Nonprescription Clinical Evaluation

- Labeling: Arlene Solbeck, M.S., interdisciplinary scientist, Division of Nonprescription Regulatory Development

- Label Comprehension Study: Susanna Weiss, PhD, social scientist, Division of Nonprescription Clinical Evaluation

4.4 Data Quality and Integrity

This reviewer is not aware of any audit processes performed on the applicant's data or analyses.

4.5 Compliance with Good Clinical Practices

For the study being reviewed herein, the sponsor who conducted the study complied with good clinical practices.

4.6 Financial Disclosures

Please refer to the medical officer review by Julie Golden, M.D. No financial disclosures were made specifically with regard to the actual use study.

5 CLINICAL PHARMACOLOGY

The results of the clinical pharmacology review were not available at the time this review was completed. This review includes general information about the pharmacokinetics and pharmacodynamics of orlistat. A more detailed review of this material can be found in the biopharmacology review by Hae Young Ahn from the Office of Clinical Pharmacology and Biopharmaceutics.

5.1 Pharmacokinetics

The chemical name for orlistat is tetrahydrolipistatin. Orlistat is a reversible lipase inhibitor that covalently binds with the active serine residues of gastric and pancreatic lipases thereby

inhibiting the hydrolysis of dietary triglycerides and the absorption of cholesterol. Orlistat inhibits dietary fat absorption by about 30%. Ninety-seven to 99% of ingested orlistat remains unabsorbed in the intestines and is excreted unchanged in the feces. The small amount of orlistat that is absorbed from the gastrointestinal tract is rapidly metabolized to pharmacologically inactive compounds during first pass through the entero-hepatic circulation. Due to orlistat's extremely low bioavailability, no clinically meaningful effects have resulted from orlistat's action on lipoprotein, hepatic, hormone-sensitive, and diacylglycerol lipases. Based on limited data, the half-life of orlistat is approximately one to two hours.[3, 5]

Orlistat treatment produces a documented decrease in the absorption of vitamins A,D, E, and beta-carotene and has the potential to decrease the absorption of vitamin K. A pharmacokinetic study demonstrated an interaction between orlistat and the absorption of beta-carotene and Vitamin E supplements. Concomitant administration of orlistat with a beta-carotene supplement reduces beta-carotene absorption by 30%. Orlistat decreases the absorption of vitamin E acetate by about 60%. Information from the integrated database for phase III orlistat trials, demonstrates that subjects taking 60 mg or 120 mg of orlistat experienced a mean decrease in serum levels of vitamins A, D, and E and beta-carotene compared to subjects taking placebo. For vitamin A (plasma retinol), the difference between placebo and orlistat 120 mg treatment groups was not statistically significant. Subjects taking 60 mg had a significantly lower rate of two consecutive vitamin level measurements below the reference normal range compared to subjects taking 120 mg orlistat. At both doses, mean levels of vitamins A, D, and E, and beta-carotene remained within the reference ranges after six months and one year of treatment.[6] As stated in the medical officer review of orlistat safety for NDA 20-766 (by Eric Coleman, M.D.), long term orlistat treatment does not appear to cause frank vitamin K deficiency as assessed with prothrombin time. However, prothrombin time is not a sensitive indicator of vitamin K deficiency and may remain normal with mild to moderate vitamin K deficiencies. Published literature suggests that fat malabsorption is associated with vitamin K deficiency.[2]

Use of orlistat within two hours of cyclosporine dosing reduces serum levels of cyclosporine.

Drug-drug interaction studies have shown that orlistat has no effect on the pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended release tablets), oral contraceptives, phenytoin, pravastatin, warfarin, or metformin.[5]

5.2 Pharmacodynamics

Alcohol does not affect the pharmacodynamics of orlistat. Please see relevant comments in section 5.1 above.

5.3 Exposure-Response Relationships

Study BM14150 was submitted under NDA 20-766. This study was a multicenter, placebo-controlled, double-blind, double-dummy, parallel group trial that evaluated weight loss achieved with the following doses of orlistat: 30 mg, 60 mg, 120 mg, and 240 mg. Weight loss achieved

with the three higher doses of orlistat was statistically superior to placebo but the weight loss achieved with the 240 mg dose was statistically the same as that achieved with the 120 mg dose.

6 INTEGRATED REVIEW OF EFFICACY

This review evaluates efficacy of orlistat 60 mg, 1 – 2 capsules taken up to TID with fat-containing meals, for weight loss among subjects using the product under actual use conditions in study NM17825. The integrated review of efficacy may be found in the medical officer review from the Division of Metabolism and Endocrinologic Products by Julie Golden, M.D.

6.1 Indication

Orlistat OTC, 60 mg is indicated for weight loss in overweight adults when used along with a reduced calorie and low fat diet. The proposed labeled duration of use is six months.

6.1.1 Methods

This review evaluates the efficacy of orlistat OTC 60mg over three months in an actual use setting based on the data from study NM17285.The efficacy data submitted to support the above indication for the proposed product is reviewed in detail by Julie Golden, M.D. from the Division of Metabolism and Endocrinologic Products.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoints for the actual use study were:

- Appropriate self-selection decision
- Appropriate use decision.

Secondary efficacy endpoints included:

- weight loss
- patterns of medicine use
- days on study medicine
- use of a multivitamin
- subjects' use of the supplementary educational materials and their usefulness.

6.1.3 Study Design

Study NM17825 was conducted by former-sponsor, Roche Consumer Health, Inc. and was designed as a pilot study in preparation for a full-scale actual use study of 60 mg orlistat. Upon study review, GlaxoSmithKline Consumer Healthcare (GSK) concluded that the study design, sample size, and resulting data adequately addressed the primary study objectives of evaluating consumer selection and usage behavior in the absence of a learned intermediary. GSK decided that another actual use study was not needed to support NDA 21887 for OTC Orlistat, 60 mg.

Study Objectives

- Primary objectives
  - To evaluate the ability of consumers to correctly select orlistat for their own use based on labeled directions.
  - To provide initial information regarding how consumers use orlistat in the absence of physician supervision, especially in terms of product dosing.

- Secondary objectives
  - Assess consumer perceptions of orlistat under actual use conditions.
  - Assess the consumer educational materials and website.

This three month, pilot actual use trial was a multi-center, pharmacy-based, open-label, three-month trial. Eighteen pharmacies, in six geographical areas of the United States (AZ, CA, MD, MN, MO, UT), participated in the study. Each pharmacy was equipped with a certified, calibrated scale. In-store advertising was the primary recruitment method. One poster and easel, and one counter-sized sign were provided to each pharmacy site. During the study, recruitment numbers were too low at seven pharmacy sites. In these areas, advertisements containing the same information as on the signs were placed in local newspapers to accelerate recruitment at these sites. The ads were run for at least two weeks.

The advertising materials targeted mildly to moderately overweight individuals without defining mildly to moderately overweight. In addition, the materials stated:

> *Enrollment in the study will take approximately 20 minutes and you will be compensated for your time.*

Reviewer comment:

1. *Subject compensation is often used as a recruitment tool in clinical studies. Compensation can create study population and data biases. In this actual use study, compensation during the study may have influenced subjects' use behaviors, such as time of discontinuation.*

Inclusion criteria

- 18 years of age and older
- Self-selected into the study
- Gives written consent to participate
- Able and available to participate in telephone follow-up interviews

Exclusion criteria

- Participated in previously conducted orlistat label comprehension studies
- Allergic to orlistat or one of its ingredients
- Previously on orlistat 120 mg (Xenical®)
- Currently treated with medication for diabetes
- Currently treated with warfarin
- Currently treated with cyclosporine
- Pregnant or breast-feeding.

Enrollment Procedures

1. First encounter

A pharmacist at each participating pharmacy served as the principal investigator for the study site. Study personnel were given a script and instructed to state only the following information to all who inquired about the study:

- Our pharmacy is part of a national research study for a weight loss drug.
- You must be at least 18 years of age to be a part of the study.
- If you wish to participate, you will need to spend about 15 – 20 minutes with the pharmacy staff today.
- You will have a chance to look at the medicine and decide if you wish to participate.
- You are free to end your participation at any time.
- All information you provide to us is confidential.

2. Self-selection

Study personnel gave the orlistat package to the subject and said, *"Imagine you are in a store and this is a new over-the-counter medicine. You can take as much time as you need to look at the packaging. Let me know when you are finished."*

The front of the orlistat package box displayed the name of the product and a list of the materials in the package, including the study drug. The back of the box displayed the Drug Facts Label.

When the subject finished examining the orlistat package, study personnel asked, *"Do you think this medication is appropriate for you to use?"* The subject's responses were recorded.

Regardless of self-selection response, study personnel collected basic demographic information from and administered the Rapid Assessment of Adult Literacy in Medicine (REALM) test to all subjects. In addition, each subject completed an eight page health survey. No informed consent procedure occurred at this time.

Reviewer comment:

1. *A general informed consent should have been obtained prior to requesting basic demographic information and completion of the health survey.*

2. *The sponsor states that training of principal investigators was done during an investigator meeting and during individual site initiation meetings that were conducted before the study began. Study pharmacy staff training occurred at the on-site pharmacy training only. This training included instruction on administration of the REALM test with verbal instruction and role play practice.*

3. Purchase decision

Once the above information was collected, study personnel asked each subject the following question, "The cost of this medication is $45 for a bottle of 90 capsules. Would you like to purchase the medication today?" Responses were recorded including reasons why subjects did not want to purchase the study drug or were undecided about whether to purchase.

Reviewer comment:

1. *This reviewer is concerned that the cost of $45 to $90 per month to use this medicine may have significantly affected the demographics of subjects who purchased study drug. While this might reflect true consumer behavior after marketing, it may prevent a thorough assessment of consumer behavior among all potential users.*

4. Informed consent and final enrollment procedures

Subjects who expressed a desire to purchase orlistat underwent informed consent with the pharmacist. Those who did not give informed consent were measured for height and weight and were compensated $20 for their time and concluded their participation.

Inclusion and exclusion criteria were applied to subjects who gave informed consent. Subjects who met exclusion criteria or did not meet inclusion criteria concluded their participation in the study after measurements for height and weight were collected, and they received $20 compensation.

Subjects who met inclusion and exclusion criteria provided personal contact information and contact information for a person who did not live with the subject but would know how to contact the subject. Height and weight measurements were collected, drug was purchased (up to three packages) and the study participant was compensated $20 for his or her time.

Weights were assessed in the pharmacy using standardized, calibrated scales. Weight loss was measured and recorded in whole pounds. Before measuring the subject, subjects were asked to empty their pockets and remove jackets, sweaters, and shoes.

Reviewer Comment:

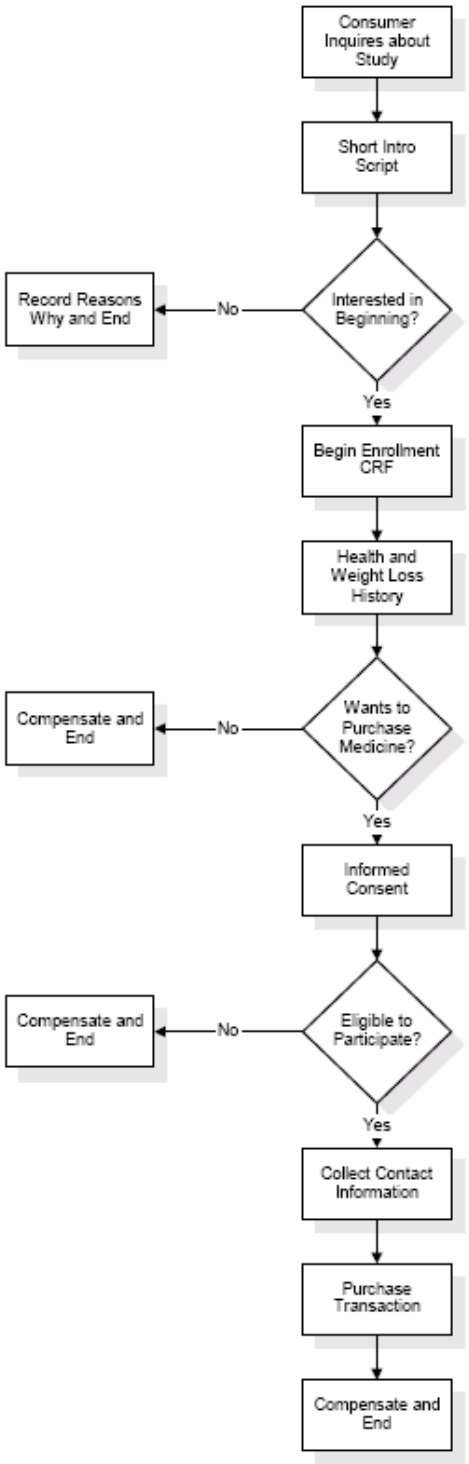
1. *Study personnel were instructed to have subjects empty their pockets and remove any jackets, sweaters, and shoes prior to being weighed at each pharmacy visit.*

2. *Comparing the flow chart summary of the pharmacy enrollment procedure, depicted below, and the sponsor's written description of the procedure, it is not clear whether subjects' heights and weights were measured before or after answering the purchase decision question.*

Figure 1 depicts a flow chart summary of the pharmacy enrollment procedure.

Figure 1:

PHARMACY ENROLLMENT PROCESS



"Thank you for your interest. Taking part in this study will take about 25-30 minutes of your time today. You are not allowed to take part in the study if you have participated in any market research survey or study for a weight loss medication in the past 12 months."

Administered by Pharmacy Staff:
- Orlistat Label and Selection Decision
- Demographics
- Measure Height and Weight
- REALM Test

Subject-Administered:
- General Health
- Weight and Family History
- Medical and Medication History
- Diet and Exercise
- Weight Loss Methods

Inclusion/Exclusion Criteria:
- 18 Years of Age or Older
- No Weight-Loss Studies or Surveys in Past 12 Months
- Not Pregnant or Breastfeeding
- Not Allergic to Orlistat or Ingredients
- Not Currently Treated with Medication for Diabetes
- Not Currently Taking Warfarin or Cyclosporine
- Consent to Participate
- Able to Participate in Phone Interviews

Includes Name, Address and Telephone Information Needed to Contact Participants for Follow-up Interviews

Actual Use Study Procedures

1. Return visits

Subjects were allowed to purchase up to three packages at any one time and could return to the pharmacy as often as desired to purchase additional medication. Each time a subject returned to the pharmacy, a weight was measured on a calibrated scale and recorded on a case report form. Any adverse events spontaneously reported by subjects during pharmacy visits were also recorded on case report forms and faxed immediately to PEGUS research for follow-up by clinical staff.

The study protocol required that subjects participate in at least one pharmacy visit after enrollment. Investigators told subjects to return to the pharmacy at the end of their study participation and to bring the medication packaging, whether empty or not. This instruction was also included in the informed consent.

Reviewer comment:

1. *The return visit form for pharmacy visits instructed pharmacy staff to count the study medication and enter the number of bottles and pills being returned. The subject was allowed to keep any medication they had purchased.*

2. *Adverse event reporting was subject driven. The mentioned event was described on the return visit form. Subjects were asked whether they adjusted their use of the study drug due to the adverse event, whether the event was treated, and when the event resolved. Space was provided for study personnel to record subject comments.*

2. Discontinuation from study

A final telephone interview was conducted any time a subject expressed an intent to end participation or stop using the study medication. Information collected during the final telephone interview included:

- Reasons subjects elected to use the medications they did
- Reasons why subjects may have elected to stop using the medication
- Subjects' insights and perceptions about the medication, their experience in the study, educational materials, the website, etc.

A clinical interviewer made a final follow-up telephone call two weeks later. Subjects were instructed to return all unused study medication to the pharmacy. Study participants who became pregnant during the study were instructed to stop using the test drug and immediately inform the investigator. All pregnancies were reported to PEGUS research within 24 hours. Pregnant patients were monitored until the end of pregnancy.

3. Data collection

Follow-up information was collected through telephone interviews scheduled 14, 30, 60, and 90 days after study. Each interview had a 10-day window for completion. During each interview window, at least eight calls were attempted before a subject was declared as "unable to contact" for that interview window. All subjects remained in the database and were called during the next interview window.

The call schedule was managed with computer assisted telephone interviewing (CATI) software. This software randomly scheduled calls to subjects according to established calling rules, kept track of call attempts and outcomes, and allowed callbacks to be scheduled at specific times. The CATI software accommodated all question types including open-ended, single choice, multiple select, and responses with dates and digits. The software guided the trained clinicians through the interview. Most of the interview questions were standardized and were displayed sequentially on the computer screen. Depending on the answer to one question, the next appropriate question would appear. The interviewer entered the subjects' responses directly into an electronic database. For open-ended or multiple selection questions, responses were recorded verbatim; however for questions requiring a yes/no response, the clinical interviewer may have summarized the subjects' response into a *yes* or ***no*** response.

Appendix 10.1 contains a complete list of CATI interview questions. The following list of questions and topics focuses on key communications during the follow-up telephone interviews:

- Was the subject using or did the subject plan to use the orlistat?
- Did the subject intend to start using the medicine? (A callback was set for this date and the subject was told that a follow-up call would be make to see if they started the medicine)
- Had the subject contacted a healthcare professional since enrollment in the study? If so, what was discussed? What was the name of the healthcare professional? No further contact information was obtained.
- Questions about use of the label, understanding the label and use of support materials provided.
- Questions about patterns of orlistat use: number of capsules per day, number of capsules per dose, doses per day, taken with meals? Were there times and reasons that the subject did not use or used a different amount of the medicine?
- Questions about multivitamin use and timing with orlistat.
- Questions about diet and exercise.
- Questions about discomforts, changes in health status (including pregnancy), hospital visits, and new medications or dietary supplements since starting orlistat.
- Questions about weight loss while using orlistat and satisfaction with the medicine.
- Questions about current and future orlistat use: Are you still using the study medicine? What was the last date you used the medicine? Do you plan to use it

again? When do you plan on using it again? (Nurse uses judgment to classify answer as will use again within 3 months of enrollment, after more than 3 months since enrollment, or don't know).

The End-of-Study Questions were asked at the post-treatment telephone interview, which was conducted approximately two weeks after a subject stopped using orlistat. The main objective of this interview was to acquire adverse event data including resolution of reported events or new events that had occurred since the last interview. The following topics and questions were asked at the End of Study telephone interview:

- Questions about whether subjects thought that orlistat was effective in helping them lose weight and whether they would purchase the drug again.
- Questions about whether subjects consulted their doctor regarding a labeled contraindication. If so, what was discussed. If not, then why.
- Many detailed questions about diet followed, reading nutritional labels, reducing fat in diet, target calories, understanding how to calculate calorie and fat information
- Questions about reasons for exercising and typical exercise done.
- Questions about use of the support materials and the website and their usefulness.
- Open-ended solicitation of other comments about the study, the medicine, or general comments.

In response to a FDA request for further information, the sponsor stated that the subject food diary was included as an educational tool in the weight loss program and was not intended for inclusion in data analysis. Therefore the diaries were not collected or reviewed.

Reviewer comment:

1. *The study materials included a food diary and a place to check off when medication was taken. There was no designated place to record taking a multivitamin. Because the sponsor's product and labeling encourage subjects to keep a diary, the diary becomes a more "naturalistic" tool. Consumers should be encouraged to keep a record of multivitamin use, because this might reinforce compliance with this labeled direction. It would have been useful for study subjects to record adverse events and use of a multivitamin in the diary.. Telephone interviews occurred two to four weeks apart and without a written record, subjects' recall may have been biased.*

2. *The ten day window for completing follow-up telephone interviews is large. Given the wide variety of information collected during these interviews, it is difficult to know how the variability in time of data collection compared with the duration of drug use might confound certain comparisons. For example, the incidence of bowel-related adverse events may be different on Day 14 and Day 24 of drug use. The sponsor does not make it*

clear whether the telephone interview data included the Study Day that the information was collected.

3. *Some of the questions asked during the telephone interviews and the response-triggered follow-up call activities may have influenced or reinforced subjects' behaviors during the study. The protocol described four telephone interviews that occurred approximately every 30 days during the study. At each interview, subjects who had not started using orlistat were questioned about their intention to start using the medicine and about when they would start using the medicine. A call back date was set for that date. These extra phone calls were not part of the data collection procedures described in the study protocol. In addition, subjects were asked about whether they were taking a multivitamin, whether they were following a diet (and whether it was supervised), and whether they were exercising. Subjects were asked about their use of label information, website information, and supplemental educational materials provided with the drug at first purchase.*

4. *It appears that far more data collection occurred through the CATI telephone interviews than through the subject-initiated pharmacy-based visits.*

4. Compensation of subjects

Subjects received compensation in the amount of $20 at the following times:

1. At the end of the enrollment visit regardless of their decision to purchase study drug.
2. Within two weeks of each interview in which they participated except for the final post-treatment telephone interview.

Subjects did not know that the money paid for orlistat during the study would be reimbursed following completion of the study.

Reviewer comment:

1. *Although subjects were unaware they would be reimbursement for drug costs at the end of the study, subject compensation throughout the course of the study may have influenced subjects' drug use and continuation behaviors during the actual use study.*

Outcome measures

1. Compliance

The pharmacy staff received drug log forms to record the dates and amounts of drug purchases for each subject and whether the subject returned the previous bottle of medication. Subjects were asked to return unused study medication at the end of the study.

2. Efficacy measurements and evaluations

Efficacy assessment was based on evaluation of the following parameters:

- Self-reported weight loss
- Measured weight loss
- Satisfaction with the study drug
- Perceived efficacy.

3. Safety measurements and evaluations

To record information about possible gastrointestinal adverse events, study personnel used a general questioning outline and Defecation Pattern Worksheet on paper as opposed to the CATI software. The Defecation Pattern Worksheet (Appendix 10.1) guided the clinical interviewers through each potential gastrointestinal adverse event. On the worksheets, the clinical interviewers recorded the intensity of each adverse event and its relationship to the study treatment. A physician reviewed each event and his or her judgment about causality. Adverse events were coded using MedDRA, version 6 (modified for orlistat-specific adverse events) and the International Nonproprietary Name Drug Terms and Procedures Dictionary for Treatments and Surgical and Medical Procedures. The following definitions were used:

- Intensity of adverse event
  - Mild: discomfort noted but no disruption of normal daily activity
  - Moderate: discomfort sufficient to reduce or affect daily activity
  - Severe: inability to work or perform normal daily activity.

- Relationship to study treatment
  - Probable
    High degree of certainty that adverse event is related to the test drug. An adverse event may be considered probable if the first three of the following criteria are present:

    - It follows a reasonable temporal sequence from administration of the drug.
    - It cannot be reasonable explained by the known characteristics of the subject's clinical state, environmental, or toxic factor, or other modes of therapy administered to the subject.
    - It disappears or decreases on cessation or reduction in dose (except with bone marrow suppression and tardive dyskinesias).
    - It follows a known pattern of response to the suspected drug.
    - It reappears upon rechallenge.

  - Possible
    Adverse event where connection with the test drug is unlikely but can not be ruled out with certainty. An adverse event may be considered probable if the first two of the following criteria are present:

    - It follows a reasonable temporal sequence from administration of the drug.
    - It may have been produced by the subject's clinical state, environmental or toxic factor, or other modes of therapy administered to the subject.
    - It follows a known pattern of response to the suspected drug.

  - Remote
    Adverse event most often meets the first two of the following criteria:

- It does **not** follow a reasonable temporal sequence from administration of the drug.
- It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It does not follow a known pattern of response to the suspected drug.
- It does not reappear or worsen when the drug is readministered.

- Unrelated
  Adverse events which are clearly and incontrovertibly due only to extraneous causes and do not meet criteria for a drug relationship as listed above.

Adverse events *not unrelated* to study drug were followed until they returned to baseline status or stabilized.

Reviewer comment:

1. *The sponsor does not explain whether the clinical interviewers were trained to assess the relationship between adverse event and study medication. It is not known whether the physician reviewing the case report form had access to the interviewer's opinion about causality and whether this information influenced the physicians' response. The sponsor does not describe how a disagreement with regard to an adverse event's relationship to study drug was managed.*

A **serious adverse event** (SAE) was any adverse event that met at least one of the following criteria:

- Fatal
- Life-threatening (immediate risk of death at the time of the event)
- In-patient hospitalization or prolongation of hospitalization
- Results in persistent or significant disability or incapacity
- Congenital anomaly
- Medically significant or requires intervention to prevent one or more of the above outcomes.

Interviewers reported serious adverse events to the sponsor within one working day. Regardless of relationship to study drug, interviewers reported any SAE that occurred during the study or within 15 days of treatment. More than 15 days after completion of treatment, interviewers continued to report SAEs believed related to the study drug. Any SAE potentially related to study drug was followed to resolution.

Data Quality Assurance

This study was conducted by Roche, Inc. and Pegus Research. Subsequently, all study data were transferred from Pegus Research to GlaxoSmithKline Consumer Healthcare (GSKCH). GSKCH data management performed an in-house review of the data.

Selected open-ended questions from the pharmacy case report forms and telephone interviews were coded for use in the data analysis. The coding was done independently by one coder from Pegus research and one from the GSKHC medical personnel. Discrepancies between the two coders were identified and resolved in house at GSKHC.

Medical history data were coded independently by two coders, a GSKHC statistician, and a GSKHC medical person. Discrepancies were identified and reconciled. GSK coders used the GSK medical dictionary (based on the WHO dictionary) for coding medications data, which were then reviewed by medical personnel.

Data Analysis Methods

1. **Sample size determination**
   The sponsor states that determination of sample size for this actual use study was based on practical considerations, rather than statistical power or margin or error. Two hundred seventy purchasers were considered sufficient for testing the study design, data collection instruments, and data analysis procedures. Roche, Inc., the drug innovator, designed this study as a pilot actual use study.

2. **Dropouts and missing data**
   Only interviews with at least one interview question answered were considered evaluable for analysis.

3. **Study population**
   The analysis populations were as follows:

1. **All screened subjects**: all subjects who completed Question 1 of the pharmacy enrollment case report form, "Do you think this medicine is appropriate for you to use?"

2. **Eligible subjects**: the subset of all screened subjects who did not have serious protocol violations. Twenty-two subjects from pharmacy site 22 were excluded due to enrollment protocol violations. Roche and Pegus research determined that subjects enrolled at this site were given additional information regarding study drug including who should use it and how it should be used. Some potential subjects were told they would be excluded before they went through the self-selection and purchase decisions.

3. **Purchasers**: the subset of eligible subjects who purchased study medicine at the initial pharmacy visit. Eligible subjects who did not purchase study medicine at the initial pharmacy visit were not allowed to return at a later time to purchase.

4. **Users**: the subset of purchasers who used at least one orlistat dose and completed at least one follow-up interview.

5. **Safety population**: the subset of all screened subjects who purchased orlistat. It included all users plus the 22 ineligible subjects from pharmacy site 22 who all purchased orlistat and subjects who purchased orlistat but did not complete any follow-up interview.

Reviewer comment:

1. *The sponsor states later in the study report that no subjects from pharmacy site 22 were included in the analysis due to protocol violation.*

2. *In a communication from the sponsor, the sponsor confirmed that the safety population included 25 subjects who purchased drug and did not use it. This increases the size of the safety population by 10% with subjects who will not experience drug-related adverse events.*

4. Statistical analysis of efficacy data

Using the *eligible subjects* population, the investigators assessed the following primary efficacy endpoints: an appropriate initial selection decision and an appropriate use decision.

- **Appropriate self-selection decision**
  The sponsor stated that the assessment of an appropriate initial selection decision was based primarily* on data collected in response to question 1, "Do you think this medicine is appropriate for you to use?" For subjects with unconditional labeled exclusions, a "no" answer was an appropriate decision. "Yes" and "don't know" were inappropriate selection decisions. For subjects with conditional labeled exclusions, appropriate selection answers included "no" and "yes" or "don't know" if the open-ended response mentioned the need to talk to a doctor.

- **Appropriate use decision**
  Among subjects with any conditional labeled exclusion, subjects made an appropriate use decision if they did not use orlistat or if they used orlistat but first consulted with a healthcare professional.

Reviewer comment:

1. *The sponsor does not state whether the subjects' healthcare providers were contacted to confirm that the subject had spoken with the healthcare provider. Neither the CATI script nor the return visit form for pharmacy visits provide for collection of healthcare provider contact information.*
2. *The label used in this study had two warnings under "Ask a doctor of pharmacist before use if you are:*
   - *Taking medicines for high blood pressure of high cholesterol/triglyceride levels. These prescription doses may need to be changed during weight loss.*
   - *Taking any other weight loss medications or supplements."*

   If subjects realized they were speaking with a pharmacist at the time of study enrollment, did they believe this fulfilled the requirement to speak with a pharmacist before using the study medicine?

Secondary efficacy parameters included:

- **Patterns of medicine use**

Patterns of use were determined from data provided by the subjects at the four follow-up telephone interviews (at 14, 30, 60, and 90 days, each with a 10 day window). The following information was collected:

- Number of capsules used per day
- Number of doses per day
- Number of capsules used per dose
- Variations in use from subject's typical pattern
- Other use patterns (percentage of day medicine was used, whether the drug was taken with meals)

- **Days on study medicine**
  At the time of the follow-up telephone interviews, the answers to three questions were used to determine how long a subject used the medicine:

  - "Are you still using the study medication?"
  - "What was the last date you used the medicine?"
  - "Do you plan to use it again?"

- **Use of a multivitamin (MVI)**
  MVI use prior to the study was assessed based on data collected data from the initial pharmacy visit. MVI use during the study was assessed using data collected only during the first follow-up telephone interview. The sponsor stated that the responses from the first interview provided the most accurate rate of vitamin use, relative to orlistat but offered no data to support this statement. On request, the sponsor submitted data documenting MVI use throughout the study. This information is discussed in the results section.

- **Subject-perceived effectiveness and satisfaction with the study medicine**
  In either the four follow-up telephone interviews or the final interview, the following perceptions were assessed using the designated questions:

  - Satisfaction with the drug: "How satisfied are you with this medicine?"
  - Future use of the drug: "Would you purchase the product again?"
  - Effectiveness of the drug: "Do you think this product is effective in helping you lose weight?"

  - Use and perceptions of educational materials:
    "Did you use any of the materials included in the orlistat package?"
    "Which did you read or use?"
    "How useful was the material?"
    "How much do you use the material?"

  - Self-reported label use and understanding:
    "Have you referred to the label for any reason?"

"When you read the label at the pharmacy, were there things you didn't understand or had questions about?"

The sponsor states that *user perceptions were summarized accordingly*.

Reviewer comments:

1. *As previously mentioned, asking the subjects questions about their use the perceptions of the educational materials and their use and understanding of the label may have biased behavior by suggesting to and reminding subjects that they should be using these materials. Ideally, these types of questions should have been reserved for the final interview.*

2. *The clinical interviewer's summary of user perceptions may not accurately reflect the subjects' responses to questions. A record of verbatim responses would have been more informative about consumer behaviors and their drivers.*

- **Weight loss during the study**
  The primary measure of weight loss was the difference between the measured pharmacy weight at enrollment and the measured pharmacy weight at the return pharmacy visit. The secondary measure of weight loss was self-reported weight loss from the follow-up telephone interviews.

Reviewer comment:

1. *The protocol only requires subjects to have a measured weight in the pharmacy at the time of study enrollment and at one pharmacy visit during the study at an unspecified time. There is no required end-of-study measured weight. Subject data was eligible for assessing efficacy and safety even if all data reported was subjectively gathered through scripted telephone interviews. The sponsor states that subjects were not given any instructions for monitoring their weight loss and no information was collected on how subjects would assess weight loss in order to maintain a naturalistic, non-interventional setting. However, this information could have been collected at the final follow-up interview without it interfering with actual use.*

All study efficacy endpoints were summarized using descriptive statistics. In addition, the following relationships were explored using the Pearson chi-square statistic to determine whether a general association existed between the two measures:

- Subject satisfaction and measured weight loss
- Subject satisfaction and defecation-related adverse events
- Subject satisfaction and number of capsules used per day
- Defecation-pattern AEs and number of capsules used per dose
- Intent for future orlistat use and measured weight loss
- Intent for future orlistat use and defecation-related adverse events.

Pearson correlation coefficients were calculated to assess the presence and linearity of the association between the two measures.

Scatter plots were used to screen for relationships between measured weight loss and starting BMI and between self-reported weight loss and starting BMI. If the scatter plot suggested a linear relationship, then a Pearson correlation coefficient was calculated to assess whether the association was statistically significant.

Reviewer Comments:

1. *This reviewer notes that:*
   - *The Type 1 error is not specified*
   - *There is no discussion of statistical adjustments for multiple comparisons*
   - *The chi-square test may not be ideal when the characteristic of interest is measured on a numerical scale (such as weight loss or number of defecation-related adverse events).*

5. Analysis of safety parameters

For the safety population, adverse events were summarized by system organ class and preferred terms. Defecation pattern change adverse events were reported and evaluated by frequency of event and whether subjects changed their orlistat pattern of use.

Reviewer Comment:

1. *The sponsor does not specify the dictionary used for adverse event reporting. A GSK dictionary based on the WHO dictionary was used for the medical history. It is not clear if the same dictionary was used for adverse event reporting.*

Treatment

All study participants who purchased drug received an OTC package of orlistat containing:

- **One to three bottles containing 90 capsules of orlistat, 60 mg**
- **Supplementary educational materials (behavioral and nutritional support)**

The directions for use instructed participants to take one to two orlistat capsules with each meal containing fat, up to three times per day for up to six months. Participants were required to participate in one pharmacy visit and five phone interviews including a post-treatment interview. The educational materials provided with the first bottle of orlistat included the following

- **The orlistat user guide, "How to Lose Weight with Orlistat"**
  - This 12-page guide offers the consumer information on how orlistat works, how much weight loss to expect, who should use orlistat and who should not use orlistat or should ask their healthcare provider first. The guide describes correct orlistat dosing in relation to meals, discusses taking a multivitamin daily, and discusses what to do if the consumer misses a dose. Potential side effects and their relationship to fat intake are generally described. The guide offers dietary suggestions and instructions on how to read a Nutrition Facts label.

- **A personal food diary**
  - Daily record of foods eaten and estimated calories and fat grams. The diary page provided a place to check off each orlistat dose when it was taken and a place to record exercise activities.

- **A pocket fat gram counter: *Harriet Roth's Fat Counter***

- **A fat gram wheel**
  A cardboard wheel that provided fat grams and portion sizes for common foods by food group.

- **A portion size information card**
  - A two-sided laminated card with tips about portions and serving sizes.

- **Orlistat Diet Success Planner**
  A 28-page binder providing lifestyle information on monitoring daily diet, eating out, and exercise. The bonder includes the following sections:

  - **Plan for success**
    This section discusses setting food goals, eating goals, and activity goals and building an awareness of food intake through tracking. Subjects are encouraged to: prepare for unexpected situations that may lead to deviations from food goals, prepare shopping lists, and plan meals for the week ahead.

  - **Diet basics**
    This section teaches subjects about proteins, carbohydrates, and fats and how to track calorie intake. Food exchange lists and sample menus are included. Healthy snacks and ideas about managing eating behaviors are suggested.

  - **Exercise your options**
    This section encourages subjects to speak with a doctor if starting a new exercise routine, offers suggestions on starting an exercise plan, and provides information about the calories burned during various physical activities.

  - **Food preparation and dining**
    This section provides guidance on buying low fat foods, reduced fat food preparation, and healthy recipe ingredient substitution. Healthy menu choices when dining out are suggested.

  - **Stay motivated**
    This section encourages subjects to reward themselves for their accomplishments, recognize personal weak points and triggers that lead to poor dietary decisions, and to ask for support.

According to the sponsor, the educational materials included in the actual use package were not tested for label comprehension prior to the actual use study. The dietary and lifestyle materials used in this study were adapted from the Xenicare® Program, the behavioral support program used with the prescription orlistat product. The Xenicare® program was researched and tested with consumers and approved by the Division of Drug Marketing, Advertising, and Communications.

Reviewer comment:

1. *This Orlistat User Guide states:*

> *"If you do not have any noticeable weight loss after three months of product use, you may wish to stop taking Orlistat and speak to your doctor."*

This statement differs from the warning in the actual use study Drug Facts label that states:

> *"Stop use and ask a doctor if you do not have noticeable weight loss after three months of product use."*

This actual use study did not assess consumer discontinuation behaviors following the 90 day drug treatment study period. This issues is discussed in more detail later in the review.

Study flow chart

Table 2: Schedule of Study Assessments							
Study visit/telephone interview	**Initial Pharmacy visit**	**Visits to Pharmacy[2]**	**Telephone Interview 1**	**Telephone Interview 2**	**Telephone Interview 3**	**Telephone Interview 4**	**Post treatment interview**
Study day	**0**		**14***	**30***	**60***	**90***	**14 days after finish treatment[4]**
Review orlistat label	●						
Self-selection question Purchase decision	●						
Medical history	●						
Demographics	●						
REALM test	●						
Measure height/weight	●	●					
Self-reported weight	●		●	●	●	●	
Informed consent	●						
Review inclusion/exclusion Criteria	●						
Collect subject contact Information[1]	●						
Dispense study medicine	●	●					
Review current medication Review health status			●	●	●	●	
Product usage information			●	●	●	●	
Exercise and diet information			●	●	●	●	
Perceptions of effectiveness			●	●	●	●	
Adverse events			●	●	●	●	●
End-of-study telephone Interview[3]			●	●	●	●	

*The protocol allowed a 10-day calling window around the scheduled date for each telephone interview.

[1]Name, address, and telephone number needed to contact subject during the follow-up period

[2]Subjects could return to the pharmacy to purchase more drug as often as desired during the three month study period.

[3]The final interview questions could be asked at any of the follow-up telephone interviews if a subject expressed intent to stop using orlistat.

[4]Post treatment interviews were only conducted if a subject stopped using orlistat less than 14 days prior to contact with a telephone interviewer.

Table 2 on the previous page summarized the schedule of study assessments. The following list of reviewer comments summarize elements of the study design that may not support this product's proposed duration of use or may make interpretation of data difficult.

Reviewer Comments:

1. *This actual use study was conducted by Roche Consumer Health, Inc. as a pilot actual use study to prepare for a full-scale actual use study to be conducted at a later date. One of the objectives of this study was to "test the planned recruitment tools enrollment processes, and data collection tools." GSK reviewed the study design and procedures and concluded that further evaluation with a larger-scale trial was unnecessary.*

2. *This actual use study evaluated consumer use of orlistat over a 90-day use period. The proposed duration of use for orlistat OTC is six months. Data collected using this study design can not provide information on consumer use and discontinuation behaviors, and consumer compliance with recommended lifestyle modifications (diet and exercise) after 90 days of use. It is often preferable for actual use studies to last longer than a product's proposed duration of use. This reviewer is concerned that consumers are likely to continue use beyond the labeled six month duration of use as a means of chronic weight regulation. Chronic use may increase the risk for adverse events if consumers do not comply with labeled instructions for effective multivitamin use and heed label exclusions.*

3. *After the enrollment date, objectively documented weights on calibrated scales were not required. The study protocol does not describe a mechanism for correlating measured weights and self-reported weights for those subjects who did come to the pharmacy and get weighed.*

4. *The protocol does not describe collection of subject diaries or the use of any data entered in the diaries to support the patterns of drug use of dietary compliance reported to the clinical interviewers during follow-up telephone interviews.*

5. *The subject diary did not provide a place to record multivitamin use or adverse events. Therefore, subject reporting of adverse events and MVI use was retrospective.*

6. *Some of the questions asked in the structured CATI interview may have served as reminders to subjects to start taking orlistat, use a MVI, and refer to the label and/or supplemental educational materials. The follow-up telephone call-back pattern was altered based on whether or not a subject had started using the study drug.*

6.1.4 Efficacy Findings

Disposition of subjects
As shown in Table 3, 703 subjects were screened, and twenty-two subjects were excluded from the user analysis due to protocol violations at one of the pharmacy sites. The remaining 681 subjects were included in the eligible population for the self-selection decision. Following the self-selection decision, 49 of the subjects were excluded from participation in the actual use portion of the study based on exclusion criteria.

Table 3: Disposition of Subjects

Population	Number of Subjects	Percentage of Subjects
All screened subjects	703	-
Subjects excluded from users analysis Due to protocol violation	22	-
Eligible subjects	681	100
Subjects excluded by study criteria	49	7.2
Subjects who chose not to purchase (does not include 49 excluded by criteria)	370	54.3
Purchasers	262	38.5
Purchasers who did not use orlistat	25	3.7
Users	237	34.8
Safety population	284	-

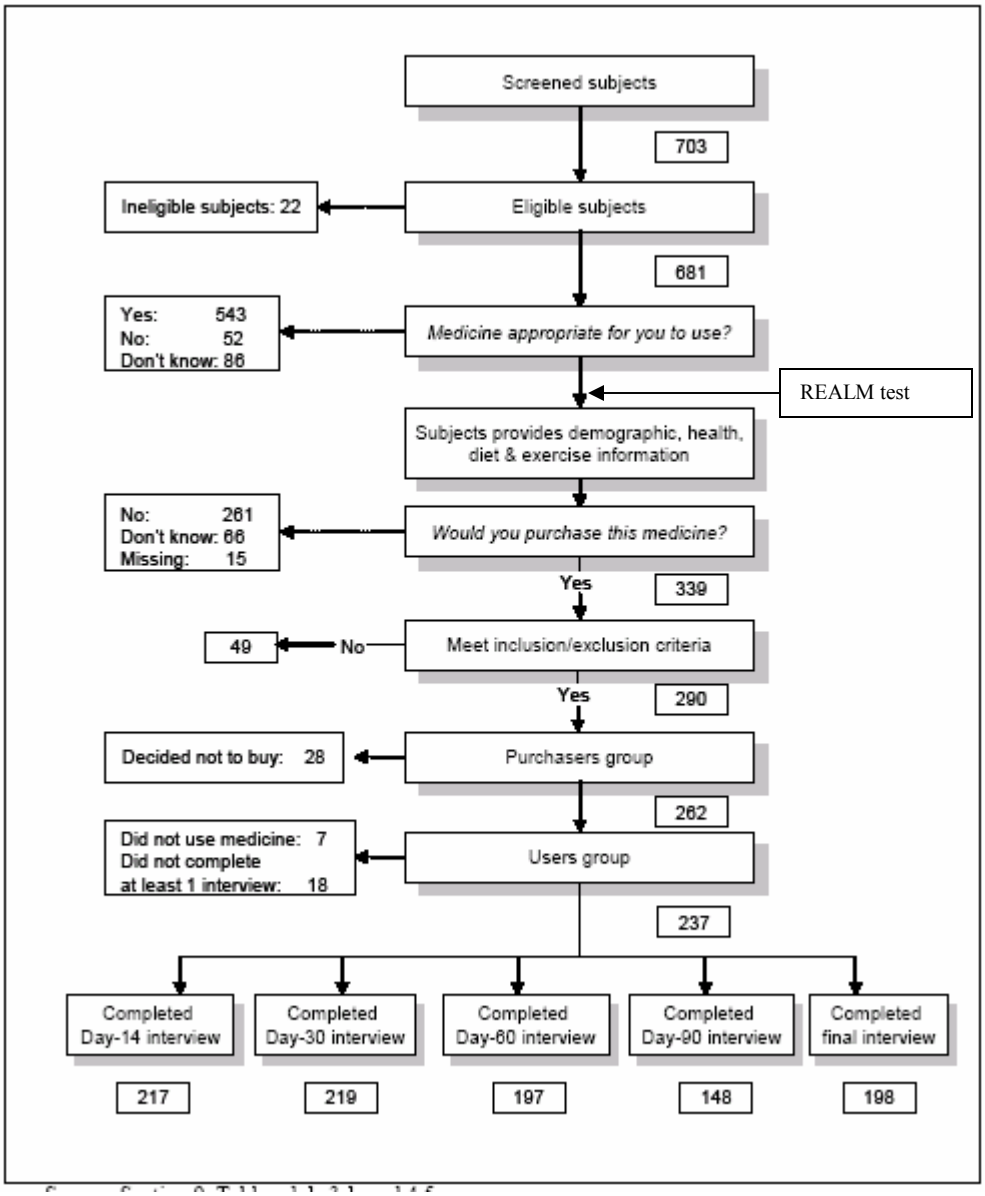
Of 681 eligible subjects, only 262 chose to purchase orlistat. Cost was the reason given by 60% of subjects for not purchasing orlistat.

Reviewer comment:

1. *The stated safety population of 284 subjects includes 25 subjects who purchased but did not use the study drug. The twenty-two subjects from the one pharmacy site with protocol violations were excluded from self-selection and actual use analysis but were included in the safety population. All 22 of these subjects purchased orlistat, and 21 of the 22 subjects used orlistat.*

Figure 2 displays the sponsor's flow chart summarizing the disposition of all screened subjects.

Figure 2: Disposition of Subjects Flowsheet



Reviewer comment:

1. *According to Figure 2, there were 18 subjects who purchased study drug but did not complete at least one interview. The sponsor does not state whether the investigators tried to follow-up with these individuals to collect safety data.*

Protocol Deviations

Roche, Inc. and Pegus Research determined that subjects enrolled at pharmacy site 22 received additional information regarding study drug, including who should use it and how it should be used. Some subjects were told they would be excluded before they made a self-selection

decision. All 22 of the subjects enrolled at this site were excluded from the efficacy analysis due to these protocol deviations. These subjects were included in the safety analysis.

Reviewer comment:

1. *It is not clear why usage data from purchasers within this group of 22 subjects were not included in the analysis. The sponsor does not state how many of the 22 subjects from this pharmacy site chose to purchase and to use study drug.*

Demographics

The purchasers and users groups had very similar demographics as did the screened and eligible populations. Table 4 compares the demographics of the study's eligible and user populations.

Table 4: Demographic characteristics of the eligible subject population and study drug user population.

Demographic	Eligible subjects (N = 681)	Users (N = 237)
Gender		
Female	79.4%	85.6%
Male	20.6%	14.4%
Mean age (years)	45.4	44.9
Age range (years)	18 – 85	18 - 75
Mean BMI (kg/m^2)	33.1 ± 6.7	32.0 ± 5.8
BMI range (kg/m^2)	20.9 – 62.6	20.9 – 53.3
Ethnicity		
Caucasian	79.3%	81.9%
Hispanic	8.1%	6.3%
African American	6.2%	2.5%
Asian	1.6%	2.5%
Native American	1.5%	1.7%
Other	3.2%	5.1%
Highest level of education		
Less than 8th grade	0.4%	0.4%
Some high school	4.3%	1.7%
High school graduate	23.5%	15.6%
Some college or tech school	40.7%	46.4%
College graduate	21.1%	25.3%
Post graduate degree	9.7%	10.5%
Missing	0.3%	0

(continued on next page)

Table 4: Demographic characteristics of the eligible subject population and study drug user population.		
Demographic	**Eligible subjects (N = 681)**	**Users (N = 237)**
(continued from previous page)		
Employment status		
Full time	45.7%	50.6%
Part time	13.7%	15.5%
Retired	14.8%	11.4%
Disabled	5.0%	4.2%
Homemaker/caregiver	9.1%	9.7%
Unemployed	8.8%	4.6%
Student	5.1%	3.8%
Other	2.3%	3.4%
Missing	0.3%	0
REALM test scores		
$\leq 3^{rd}$ grade (score 0 – 18)	0.1%	0.4%
4^{th} – 6^{th} grade (score 19 – 44)	1.5%	0.4%
7^{th} – 8^{th} grade (score 45 – 60)	6.5%	3.4%
low literate subtotal (score ≤ 60)	8.1%	4.2%
literate, $> 8^{th}$ grade (score ≥ 61)	91.5%	95.8%
Use of weight management drug or supplement in past 12 months	22.8%	27.4%

More than three quarters of the eligible subjects were women, and women comprised 85% of the user population. For comparison, the pooled subject population from the Phase III clinical trials for Xenical® was 78 – 83% female. Among eligible male subjects, 24.3% chose to use orlistat, whereas 37.5% of eligible female subjects chose to use orlistat. Ages of orlistat users ranged between 18 and 75 years, with a mean of 45 years of age. The mean baseline BMI among eligible subjects was 33.1 kg/m^2, and the mean baseline BMI was 32.0 kg/m^2 among orlistat users. For both subject groups, the BMI range extended from normal weight (20.9 kg/m^2) to morbidly obese (53.3 – 62.6 kg/m^2). The user population was predominantly Caucasian (82%) with African-Americans underrepresented (2.5%). Hispanics and Asians were also underrepresented, comprising 6.3% and 2.5% of the user population respectively. For comparison, the 2002 U.S. Census Bureau reports that the civilian, noninstitutionalized U.S. population is 13% Blacks, 13.3% Hispanics, and 4.4% Asian/Pacific islander.[3]

The user population was relatively well educated with 25% completing a college degree and nearly 50% having some college or technical school education. The sponsor did not clarify whether subjects with an Associate degree were considered college graduates. Only 2% of the subjects using orlistat did not graduate from high school. For comparison, according to the U.S. Census Bureau report on educational attainment, 15.8% of the U.S. civilian, noninstitutionalized population aged 18 years and older are not high school graduates.[3] Consistent with this educational history, 96% of orlistat users read at better than an eighth grade level. The low literacy user population consisted of ten subjects, 4% of the orlistat users in this study.

English was the primary language for 96.2% of eligible subjects and 95.8% of users. Spanish was the primary language spoken by 1.9% of eligible subjects and 1.7% of users. Users whose primary language was German, Chinese, or another language comprised 2.0% of the eligible subject population and 2.9% of the users population.

Weight demographics and perceptions
As illustrated in Table 5, more than 90% of orlistat users were either overweight or obese as defined by BMI. Although they represent only 7.6% of the user population, it is noted that 18 normal weight individuals chose to use a medicine indicated for overweight individuals. As shown in Table 6, none of these 18 normal-weight orlistat users considered themselves average weight for their build and height. Five orlistat users (2.1%) perceived themselves as underweight.

Table 5: BMIs of eligible subjects and orlistat users at baseline

BMI (kg/m^2)	Eligible subjects (N = 681)	Orlistat Users (N = 237)
< 25	49 (7.2%)	18 (7.6%)
25 – 29.9	181 (26.6%)	76 (32.1%)
≥ 30	444 (65.2%)	143 (60.3%)
Missing data	7 (1.0%)	0

Table 6: Self perception of appropriateness of body weight based on completion of the following statement: "I consider myself to be…."

Answer	**Eligible subjects** (N = 681)	**Purchasers** (N = 262)	**Users Group** (N = 237)
Moderately underweight	3.5%	1.5%	1.3%
Slightly underweight	1.6%	0.8%	0.8%
Average weight for height and build	0.9%	0	0
Mildly overweight	17.3%	18.3%	18.6%
Moderately overweight	57.4%	62.6%	62.4%
Severely overweight	18.2%	16.4%	16.5%
Other	0.3%	0.4%	0.4%
Missing	0.7%	0	0

Table 7 displays baseline BMI information for orlistat users by gender and age. In subject age groups that contained at least ten subjects, the mean baseline BMI was between 30.3 and 33.2 kg/m^2. All eligible male subjects were overweight or obese. Eighteen of 202 (8.9%) female subjects who used orlistat were not overweight.

Table 7: Baseline BMI among orlistat users by gender and age								
Age Group (yrs)	Subjects		Mean BMI (kg/m^2)		BMI Range (kg/m^2)		Standard Deviation	
	♂	♀	♂	♀	♂	♀	♂	♀
18 – 20	2	11	35.2	32.5	32.7 – 37.7	24.0 – 49.9	3.54	7.86
21 – 25	1	5	33.6	28.5	33.6 – 33.6	25.1 – 31.3	-	2.57
26 – 30	2	8	34.6	28.2	28.0 – 41.2	21.7 – 36.2	9.33	5.16
31 – 35	4	25	38.7	33.2	31.7 – 47.9	25.4 – 45.4	6.91	5.00
36 – 40	2	30	30.9	31.6	28.3 – 33.5	22.3 – 47.3	3.68	6.26
41 – 45	5	34	35.7	31.6	31.3 – 41.3	20.9 – 45.8	4.95	5.18
46 – 50	2	27	40.9	30.3	36.5 – 45.2	21.8 – 48.1	6.15	6.14
51 – 55	3	17	33.6	31.8	32.5 – 35.4	23.7 – 53.3	1.59	6.98
56 – 60	5	25	35.1	31.2	32.1 – 37.3	24.1 – 45.0	2.03	5.69
61 – 65	2	10	36.3	32.5	32.0 – 40.6	25.2 – 37.8	6.08	4.64
66 – 70	3	5	29.9	34.3	27.9 – 32.0	27.0 – 52.3	2.05	10.37
71 – 75	3	5	31.5	30.4	27.8 – 33.8	25.8 – 32.4	3.24	2.66

Reviewer comment:

1. *All five subjects who considered themselves underweight made an incorrect self-selection decision based on indication for use. Based on actual measured weight, 8.9% of female subjects choosing to use orlistat made incorrect self-selection and use decisions. This reviewer notes that these individuals represent a small portion of the consumer population that may misuse this medication in an over-the-counter environment. Specific demographic information regarding non-overweight subjects who used orlistat has been requested from the sponsor but has not yet been received.*

Self-selection and Use Decisions: Assessment of Primary Endpoints

The pivotal self-selection question was, "Do you think this medication is appropriate for you to use?" Of 681 eligible subjects, 543 (79.7%) answered yes and 52 (7.6%) answered no. Eight-six (12.6%) subjects said they did not know or were not sure.

Subjects who thought that orlistat was not appropriate for them to use (N = 52) gave the following reasons:

- Unconditional exclusions: 19 (36.5%)
- Conditional exclusions: 19 (36.5%)
- Side effects: 7 (13.5%)
- Product unknown/untested: 4 (7.7%)
- Don't need the product: 4 (7.7%)
- Talk to a health care professional (HCP) first: 3(5.8%)
- Other: 7 (13.5%).

Subjects who were unsure or did not know if orlistat was appropriate for them to use offered the following reasons:

- Conditional exclusion (39.5%)
- Needed to talk to a HCP first (29.1%)
- Product unknown and untested/ not enough information to make a decision (23%)
- Unconditional exclusion (6%)
- Possible side effects (6%).

Among the 543 subjects who thought that orlistat was appropriate for them to use, 317 (58.4%) chose to purchase the drug. These figures are shown in Table 8. Two subjects, who thought that orlistat was not appropriate for them to use and twenty subjects, who were unsure, purchased the drug anyway. Approximately half of the subjects who were unsure whether the study drug was appropriate for them to use did not want to purchase orlistat but the other half of these subjects either wanted to purchase study drug or didn't know what they wanted to do. The study protocol did not provide a mechanism whereby a subject could consult with their healthcare professional, as stated in the product label, and then return to purchase study drug (an actual use situation). In addition, the sponsor did not describe any mechanism used to follow-up on subject contact with a HCP during the study other than by subjective report. An appropriate self-selection decision was not always followed by an appropriate purchase decision, but it is unclear how often this actually occurred.

Table 8: Responses to self-selection and purchase questions

Eligible population, N = 681		Would you like to purchase the medication (today)?				
		Yes	No	Don't Know/unsure	Missing	Total
Do you think this medication is appropriate for you to use?	**Yes**	317	170	44	12	**543 (79.7%)**
	No	2	47	1	2	**52 (7.6%)**
	Don't Know/unsure	20	44	21	1	**86 (12.6%)**
	Total	339 (49.8%)	261 (38.3%)	66 (9.7%)	15 (2.2%)	**681 (100%)**

Purchasers:
93.5% of purchasers thought the medication was appropriate for them to use.
0.6% of purchasers thought the medication was not appropriate for them to use.
5.9% of purchasers were unsure whether the medication was appropriate for them to use.

Subjects who did not want to purchase orlistat provided the following reasons:

- Cost: 153 (58.6%)
- Product unknown/untested: 23 (8.8%)
- Talk to a HCP: 17 (6.5%)

- Unconditional exclusions: 13 (5.0%)
- Side effects: 12 (4.6%)
- Timing not good: 10 (3.8%)
- Conditional exclusions: 8 (18.0%)
- Other: 47 (18.0%)

Subjects who were uncertain about purchasing orlistat provided the following reasons:

- Cost: 20 (30.3%)
- Product unknown/untested: 16 (24.2%)
- Talk to a HCP: 11 (16.7%)
- Conditional exclusions: 3 (4.5%)
- Side effects: 3 (4.5%)
- Unconditional exclusions: 2 (3.0%)
- Timing not good: 2 (3.0%)
- Other: 10 (15.2%)

Among the 681 eligible subjects, 44 subjects were unsure if orlistat was appropriate for them to use and chose not to purchase medicine at the time of enrollment. An additional 44 subjects stated that orlistat was appropriate for them to use but were unsure whether they wanted to purchase orlistat at the time of enrollment.

Reviewer comment:
Some of these individuals (9.7% of the eligible population), if given the opportunity, may have consulted with a HCP and returned to purchase drug at a later date. However, the study protocol did not allow for this.

As mentioned earlier, only 0.4% of eligible study subjects had a less than eighth grade education, but 8.1% of the eligible population was of low literacy on the REALM test. Among the 55 eligible subjects of low literacy, only ten chose to purchase and use orlistat. One of these users was not overweight with a baseline BMI = 20.9 kg/m^2. Four normal weight, low literate females wanted to use orlistat but did not purchase. Three of these subjects clearly stated that they could not purchase due to cost or had to wait until they were paid. At least 27 of the low literacy non-purchasers did not buy study drug due to the cost. Two others wanted to return another day to purchase but did not specifically mention cost issues. Nine subjects who wanted to purchase drug had uncondititonal labeled exclusions and were not allowed to purchase.

Reviewer comment:

1. *By not allowing subjects with conditional exclusions to consult a healthcare professional prior to purchase and then return to purchase orlistat, the purchasers and users group may have been biased toward label noncompliance. The users population may have excluded subjects who made a correct self-selection decision but did not want to purchase drug until their HCP said they could use it. However, the users population did include subjects who made an incorrect self-selection decision regarding use and purchase on that first day.*

Labeled Exclusions and Subjects' Self-Selection and Use Decisions
Appendix 10.4 contains the Drug Facts label used during actual use study, NM17285. Appendix 10.5 contains the Drug Facts label submitted with NDA 21-887. These labels differ most significantly in warning content and classification. Table 9 offers a brief overview of the differences in labeled exclusions between the two labels. Table 10 contains a comprehensive description of differences in each section of the actual use study and NDA Drug Facts labels.

Table 9: Comparison of Unconditional (U) and Conditional (C) Labeled Exclusions

Labeled exclusion	Actual use study label	NDA label
Allergic to ingredients	U	U
Taking cyclosporine	U	U
Taking warfarin	U	C
Taking diabetes medicine	U	C
Not overweight	absent	U
Problems absorbing food	C	U
Problems absorbing food	C	C
Kidney stones	absent	C
Diabetes	C	absent
High blood pressure	C	absent
High cholesterol/triglycerides	C	absent
More than 30 pounds to lose	C	absent
On diet recommended by doctor	C	absent
Taking another weight loss medicine	C	C
Pregnant or breastfeeding	C	U

The NDA label no longer contains conditional exclusions for diabetes, hypertension, and high cholesterol and/or triglycerides. The conditional exclusions for subjects on a doctor-recommended diet or with more than 30 pounds to lose have also been removed. The unconditional exclusion for warfarin has become a conditional exclusion and malabsorption problems and pregnancy/breastfeeding have become unconditional exclusions. New warnings that appear on the NDA label include a conditional warning about kidney stones and an unconditional warning for those who are not overweight. These new label communications were not assessed in this actual use study because they were added by GSK after Roche completed the study. The labeled conditions in the label submitted with the NDA are evaluated in the label comprehension study conducted subsequently and submitted with this NDA. The label comprehension study is reviewed by Susanna Weiss, PhD.

The prescription label for Xenical® (orlistat, 120 mg) includes the following labeled contraindications, warnings, and precautions:

Contraindications:

- Chronic malabsorption syndrome
- Cholestasis

- Known hypersensitivity to active or inactive ingredient

Warnings:

- Organic causes of obesity (e.g. hypothyroidism) should be excluded before prescribing Xenical.
- Preliminary data indicate a reduction in cyclosporine plasma levels when Xenical was coadministered with cyclosporine. Therefore Xenical and cyclosporine should not be coadministered. To reduce the chance of a drug-drug interaction, cyclosporine should be taken at least 2 hours before or after Xenical in patients taking both drugs. More frequent cyclosporine level monitoring should be considered.

Precautions:

- Patients should be advised to adhere to dietary guidelines. Gastrointestinal events may increase when Xenical is taken with a diet high in fat.
- Patients should be strongly encouraged to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition, because Xenical has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene. The supplement should be taken once a day at least 2 hours before or after the administration of Xenical, such as at bedtime.
- Some patients may develop increased levels of urinary oxalate following treatment with Xenical. Caution should be exercised when prescribing Xenical to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis.
- Weight-loss induction by Xenical may be accompanied by improved metabolic control in diabetics, which may require a reduction in the dose of oral hypoglycemic medication.

As shown in Table 10, both versions of the proposed orlistat OTC label contain a maximum duration of use of six months. This actual use study evaluated consumer use of orlistat over 90 days (3 months).

Reviewer comment:

1. *The proposed labeled duration of use for orlistat OTC is six months. However, this actual use study provides data on only three months of consumer use. There is no data available on weight loss after three months of use or consumer continuation and discontinuation behavior based on labeled duration of use or reaching a normal weight BMI. There is no information about the concomitant use of a multivitamin after three months of use or the use of appropriate dietary modifications.*

2. *The self-selection and use decisions made by subjects regarding label elements that are no longer part of the orlistat OTC NDA label are important from a consumer compliance perspective but not from a safety perspective.*

3. *The proposed Drug Facts label for orlistat OTC does not address the issue raised in prescription labeling about eliminating organic causes of obesity (such as hypothyroidism) before using orlistat.*

4. *The proposed Drug Facts label for orlistat OTC does not explain that use of orlistat decreases the absorption of fat soluble vitamins (A, D, E, and potentially K) and beta-carotene. Consumer compliance with correct use of a multivitamin with orlistat might be positively influenced by information explaining why the multivitamin is recommended.*

Table 11 contains a detailed account of correct and incorrect self-selection and use decisions by label element. A discussion of these data follows the table.

Table 10: Drug Facts Label Comparison		
Key element	**Drug Facts label from actual use study**	**Drug Facts label submitted with NDA**
Use	To promote weight loss when taken with a reduced calorie diet	Promote weight loss in overweight adults when used along with a reduced calorie and low fat diet
Warnings: ***Do Not Use***	▪ If you are allergic to orlistat or any of the ingredients in this product. ▪ If you are taking cyclosporine (a drug given after organ transplant surgery), warfarin (blood thinning medicine) or prescription medicines for diabetes	▪ If you are allergic to any of the ingredients in orlistat capsules ▪ If you are taking cyclosporine (a drug given after organ transplant) ▪ If you have been diagnosed with problems absorbing food ▪ If you are not overweight
Warnings: ***Ask a doctor before use if you have***	▪ Problems absorbing food (malabsorption) ▪ Gallbladder problems ▪ More than 30 pounds to lose ▪ Been given a diet recommended by a doctor ▪ Diabetes, high blood pressure, or high cholesterol/triglyceride levels	▪ Gallbladder problems or kidney stones
Warnings: ***Ask a doctor or pharmacist before use if you are***	▪ Taking medicines for high blood pressure or high cholesterol/triglyceride levels. These prescription doses may need to be changed during weight loss. ▪ Taking any other weight loss medications or supplements.	▪ Taking medicine for diabetes. Your medication dose may need to be adjusted during weight loss. ▪ Taking warfarin (blood thinning medicine) ▪ Taking other weight loss drugs
Warnings: ***Stop use and ask a doctor***	▪ You have an allergic reaction to the product ▪ You do not have noticeable weight loss after 3 months of product use.	None.
Warnings: ***If pregnant or breastfeeding***	▪ Ask a health professional before use.	▪ No not use.
Directions	▪ Before using this product, please read the enclosed user's guide for complete directions and other important information. ▪ This product is for mild to moderately (up to 30 pounds) overweight adults 18 years and older ▪ Take 1 to 2 capsules (60 mg) with each meal containing fat, up to 3 times a day. ▪ This product can be used for up to 6 months of continuous use. If you would like to continue use beyond 6 months, please read the enclosed user's guide.	▪ For overweight adults 18 years and older ▪ Before using this product, read the enclosed Companion Guide for complete directions and other important information ▪ 1 to 2 capsules with each meal containing fat. Start with 1 capsule. After you have gained experience with choosing meals that contain less than 30% fat, you can increase to 2 capsules for maximum weight loss. ▪ Do not exceed 6 capsules daily ▪ Continue daily use for up to 6 months. If you have not reached your weight loss goal by 6 months, talk to your doctor. ▪ To ensure adequate vitamin absorption, you should take a multivitamin once a day, 2 hours before or after taking orlistat capsules.
Other information	▪ This product can reduce the level of vitamins in your body. Therefore, you should take a daily multivitamin 2 hours before or 2 hours after taking this product.	▪ Storage information only

Table 11: Summary of self-selection and use decisions among actual use study subjects with one or more labeled exclusions (N = 465)						
Actual Use Study Label Exclusion criterion (U = unconditional) (C = conditional)	**Subjects with labeled exclusion(s)** (N = 465)	***Do you think this medication is appropriate for you to use?***	**Noted labeled condition or need to talk to doctor**	**Appropriate self-selection decision**	**Appropriate use decision**	**NDA Label Exclusion Criteria** (bold if different from actual use study label)
Allergic to ingredients (U)	0	Yes 0	N/A	N/A	N/A	Unconditional
		No 0	N/A			
		DK* 0	N/A			
Taking cyclosporine (U)	2 (0.3%)	Yes 1 (50.0%)	N/A	50.0%	N/A	Unconditional
		No 1 (50.0%)	N/A			
		DK 0 (0%)	N/A			
Taking warfarin (U)	14 (2.1%)	Yes 6 (42.9%)	N/A	50.0%	N/A	**Conditional**
		No 7 (50.0%)	N/A			
		DK 1 (7.1%)	N/A			
Taking diabetes medicine (U) †	46 (6.8%)	Yes 24 (52.2%)	N/A	34.8%	N/A	**Conditional**
		No 16 (34.8%)	N/A			
		DK 6 (13.0%)	N/A			
Problems absorbing food (C)	12 (1.8%)	Yes 9 (75.0%)	0	16.7%	0% (0 of 1)	**Unconditional**
		No 1 (8.3%)	1			
		DK 2 (16.7%)	1			
Gallbladder problems (C)	25 (3.7%)	Yes 13 (52.0%)	0	40.0%	28.6% (2 of 7)	Conditional
		No 2 (8.0%)	2			
		DK 10 (40.0%)	8			
High blood pressure (C)	166 (24.4%)	Yes 101 (60.8%)	15	44.0%	38.9% (21 of 54)	**Absent**
		No 30 (18.1%)	23			
		DK 35 (21.1%)	28			
High cholesterol/triglycerides (C)	147 (21.6%)	Yes 94 (63.9%)	19	46.3%	42.9% (21 of 49)	**Absent**
		No 29 (19.7%)	21			
		DK 24 (16.3%)	20			
More than 30 pounds to lose (C)	346 (50.8%)	Yes 261 (75.4%)	15	21.1%	23.7% (27 of 114)	**Absent**
		No 34 (9.8%)	26			
		DK 51 (14.7%)	24			
On diet recommended by doctor (C)	48 (7.0%)	Yes 23 (47.9%)	5	54.2%	50.0% (5 of 10)	**Absent**
		No 12 (25.0%)	10			
		DK 13 (27.1%)	9			
Taking another weight loss medicine (C)	33 (4.8%)	Yes 28 (84.8%)	2	12.1%	25.0% (3 of 12)	Conditional
		No 1 (3.0%)	1			
		DK 4 (12.1%)	1			

Clarifications from Table 11:
* DK = don't know
** Based on data provided by the sponsor, the pregnancy and breastfeeding label warning was not evaluated during the actual use study.
† In the label used for the actual used study, diabetes is a labeled condition under ***Ask a doctor before use***. This element of the label was not evaluated in the self-selection or use decision-making processes. The use of diabetes medicines element was tested.

Table 11 illustrates appropriate self-selection decisions among 12 – 54% of various subject cohorts based on labeled exclusion. Fifty percent of subjects taking cyclosporine and warfarin correctly recognized that orlistat was not appropriate to take; however, 50% purchased and used the drug. Among conditional exclusions, correct self-selection decisions included subjects who chose to purchase the drug but stated that they needed to speak to a HCP before using it. Sixty-five percent of subjects on diabetes medications, 60% of those with gall bladder problems, 56% of subjects with hypertension, and 54% with elevate serum lipids made incorrect self-selection decisions. Nearly eighty percent of subjects with more than 30 pounds to lose and nearly 90% of subjects using other weight loss agents made incorrect self-selection decisions based on the label. Smaller percentages of subjects with conditional labeled exclusions chose to use orlistat; however, based on subjects' reasons for choosing not to purchase, this decision was more likely motivated by drug cost rather than reconsideration of the label warning.

Table 12 displays the self-selection and use decisions among the eligible, low literate population. Appropriate decision rates for the overall study population are included for comparison for each label element.

Table 12: A comparison of appropriate self-selection and use decision rates between low literate subjects and the general study population

Actual Use Study Label Exclusion criterion (U = unconditional) (C = conditional)	**Appropriate self-selection decision**		**Appropriate use decision**	
	Low-literate	**General**	**Low literate**	**General**
Taking cyclosporine (U)	No subjects	50%	N/A	N/A
Taking warfarin (U)	No subjects	50%	N/A	N/A
Taking diabetes medicine (U)	2 of 11 → 18.2%	34.8%	N/A	N/A
Problems absorbing food (C)	0 of 1 → 0%	16.7%	0 of 1	0%
Gallbladder problems (C)	No subjects	40.0%	No purchasers	28.6%
High blood pressure (C)	9 of 15 → 60.0%	44.0%	0 of 2	38.9%
High cholesterol/triglycerides (C)	7 of 11 → 63.6%	46.3%	0 of 2	42.9%
More than 30 pounds to lose (C)	9 of 35 → 25.7%	21.1%	0 of 6	23.7%
On doctor-recommended diet (C)	4 of 6 → 66.7%	54.2%	No purchasers	50.0%
Taking another weight loss medicine (C)	0 of 3 → 0%	12.1%	No purchasers	25.0%

This reviewer acknowledges that labeling submitted with the NDA (see section 10.4) no longer includes hypertension, elevated serum lipids, more than 30 pounds to lose, or a doctor-

recommended diet in the label warnings. From a safety perspective, the poor compliance on these label elements is less concerning, as there are no clinical data to suggest that overweight individuals with these conditions are at increased risk using orlistat compared to individuals without these conditions. The warfarin warning is a conditional exclusion on the new label due to the decreased absorption of vitamin K that occurs with orlistat use. In clinical studies, no changes in prothrombin times have been seen in patients concomitantly using orlistat and warfarin, and pharmacokinetic studies have shown no interaction between the two drugs. However, the behavioral disregard for the label warnings on this product is concerning, as it may reflect a general behavioral pattern among consumers who would use this product regardless of actual label warnings

Reviewer comment:

1. *It is difficult to extrapolate results from this actual use study to the general population of consumers who might use orlistat OTC. The demographics of the study population do not accurately reflect the racial and educational make-up of the American people; the duration of the study is half the proposed duration of use on the label; the proposed label submitted with the NDA is different, both in content and organization, than the label studied in NM 17285; the user population contained only 237 subjects; and the study design did not provide objective measurements of weight loss from the beginning to the end of the study or accurate, prospective documentation of multivitamin use or adverse events.*

2. *It is interesting to note that for certain conditional labeled exclusions (high blood pressure, high serum lipids, more than 30 pounds to lose, and using a doctor-recommended diet) the low-literate population made more correct self-selection decisions than the general study population. This reviewer wonders if more literate (and possibly more highly educated) individuals consider themselves well-informed consumers who are knowledgeable enough to bypass or dismiss label instructions to consult a healthcare provider for guidance on the use of an OTC medicine.*

Subject Use Behaviors

During the actual use study, subjects used orlistat for an average of 67 days, but the range extended from zero days to 90 days. Subjects used orlistat 5 – 100% of the days during their duration of use, with a mean use of 86 – 91% of days. This information is displayed in Table 13.

Table 13: Days on Orlistat

Mean	67.1 ± 26.4
Median	77.5
Range	3 - 90
% days subjects used orlistat*	
Mean	86.0 – 90.5%
Median	95.0 – 100.0%
Range	5 – 100%

* sponsor calculated data from each of the 4 telephone interview cohorts separately

As shown in Table 14, only one subject admitted to using more than six capsules per day at any time during the study. If all subjects with missing data were presumed to have taken more than six capsules per day, then no more than 2.7% of subjects over-used orlistat during the study. Ninety-five to 97% of subjects took orlistat with meals as directed, and 97% of subjects took one to three orlistat doses per day.

Table 14: Summary of Typical Orlistat Usage Behavior During Study

Parameter	Interview data			
	Day 14 (N = 217)	Day 30 (N = 219)	Day 60 (N = 197)	Day 90 (N = 148)
Average number of capsules per day				
0 capsules	1 (0.5%)	1 (0.5%)	1 (0.5%)	0
1 capsules	15 (6.9%)	15 (6.8%)	28 (14.2%)	15 (10.1%)
2 capsules	42 (19.4%)	51 (23.3%)	48 (24.4%)	24 (16.2%)
3 capsules	105 (48.4%)	87 (39.7%)	61 (31.0%)	61 (41.2%)
4 capsules	16 (7.4%)	29 (13.2%)	28 (14.2%)	20 (13.5%)
5 capsules	18 (8.3%)	14 (6.4%)	6 (3.0%)	10 (6.8%)
6 capsules	19 (8.8%)	18 (8.2%)	21 (10.7%)	13 (8.8%)
7 capsules or more	0	0	0	1 (0.7%)
missing or no answer	1 (0.5%)	4 (1.8%)	4 (2.0%)	4 (2.7%)
Documented overuse	0	0	0	0.68%
Average doses per day				
0 doses	1 (0.5%)	1 (0.5%)	1 (0.5%)	0
1 dose	19 (8.8%)	21 (9.6%)	36 (18.3%)	21 (14.2%)
2 doses	64 (29.5%)	81 (37.0%)	76 (38.6%)	56 (37.8%)
3 doses	128 (59.0%)	109 (49.8%)	80 (40.6%)	67 (45.3%)
4 doses or more	4 (1.8%)	4 (1.8%)	1 (0.5%)	0
missing or no answer	1 (0.5%)	3 (1.4%)	3 (1.5%)	4 (2.7%)
Usual number of capsules per dose				
0 capsules/dose	1 (0.5%)	1 (0.5%)	1 (0.5%)	0
1 capsule/dose	153 (70.5%)	148 (67.6%)	129 (65.5%)	88 (59.5%)
2 capsules/dose	61 (28.1%)	64 (29.2%)	64 (32.5%)	55 (37.2%)
3 or more capsules/dose	0	1 (0.5%)	0	1 (0.7%)
Missing or no answer	2 (1.0%)	5 (2.3%)	3 (1.5%)	4 (2.7%)
Subjects taking orlistat with meals	211 (97.2%)	211 (96.3%)	192 (97.5%)	141 (95.3%)
Subjects still using orlistat	206 (86.9%)	204 (86.1%)	150 (63.3%)	110 (46.4%)

During the course of the study, the percentage of subjects using two orlistat capsules per dose increased from 28.1% at study day 14 to 37.2% at study day 90. At study day 90, 46.4% of subjects were still using orlistat with 29.1% using more than three capsules per day but only 8.8% using six capsules per day. It is important to note that this use information was obtained through the structured telephone interviews. The sponsor did not offer supporting data obtained at pharmacy visits or through review of subject diaries to support this information.

During the actual use study, some subjects varied their orlistat use patterns for a variety of reasons as shown in Table 15. At some time during study participation, 50 – 57% of subjects took fewer capsules than usual. Nearly 60% of the time, subjects used fewer orlistat capsules

than usual because they ate a low fat or small meal. More than one quarter of the time, subjects forgot to take their orlistat or were too busy to bother. Fifteen percent of the time, subjects took less orlistat than usual because they missed a meal.

Table 15: Variations From Typical Orlistat Use Pattern

Behavioral variation	Subjects*	Explanations
Took fewer capsules than usual	50.0 – 57.1%	Meal low fat or small (57.9%) Forgot/too busy (27.9%) Missed a meal (15.2%) Not convenient (11.2%) Took less at beginning (10.7%) Adverse side effects (9.1%) Medical procedure/ other meds (1.0%) No more orlistat (1.0%)
Took more capsules than usual	24.4 – 30.5%	Meal high fat or large (68.5%) Took more at beginning (7.3%) To try it/see if different (6.5%) Not losing weight (1.6%) Proximity of bathroom (0.8%) Other (36.3%)
Times when orlistat not used	46.5 – 68.5%	Forgot (35.2%) Medicine not on hand (27.6%) Meal low fat or small (19.1%) Side effects (17.1%) Other medical issues (16.1%) Fear of side effects/away from home (15.1%) Missed a meal (12.6%) Ran out of medicine (8.0%) Medicine not working (2.0%) Cost (1.5%) Drug interactions (0.5%) Other (29.1%)

* range of subjects given as percentage was tabulated by sponsor for each telephone interview

Twenty-four to 31% of subjects used more orlistat capsules than usual at some point during the actual use study. Almost 70% of the time, subjects used more orlistat because they ate a large meal or a meal high in fat.

Reviewer comment:

1. *Based on orlistat's mechanism of action, it is recommended to use the product in combination with a low-fat diet to minimize adverse events. It is possible that these subjects did not understand this element of the labeling. It is also possible that subjects' prioritized the avoidance of absorbed fat calories over the avoidance of drug-associated gastrointestinal adverse events.*

From a safety perspective, subjects' use patterns of orlistat with a daily multivitamin (MVI) are of interest. Laboratory studies completed during the pivotal studies for the orlistat 120 mg approval demonstrated a statistically significant decline in the serum levels of fat soluble vitamins (specifically vitamins A, D, and E) and beta carotene. The decrease was not clinically significant even during studies lasting two years. Due to these decreases in fat-soluble vitamins, a daily MVI is recommended while using orlistat.

Table 16: Multivitamin (MVI) use among orlistat users (N = 237) prior to and during the study

MVI use parameter	Telephone interview			
	Day 14 (N = 217)	**Day 30 (N = 219)**	**Day 60 (N = 197)**	**Day 90 (N = 148)**
Subjects currently using MVI	163 (75.1%)	178 (81.3%)	163 (82.7%)	127 (85.8%)
Subjects taking MVI daily or more than once daily	156 (71.9%)	173 (79.0%)	158 (80.2%)	120 (81.1%)
Subjects taking MVI more than 2 hours before or after orlistat	83 (38.2%)	98 (44.7%)	88 (44.7%)	79 (53.4%)

In order for the MVI components to be effectively absorbed, the MVI should be taken at least two hours before or two hours after orlistat. As shown in Table 16, during the course of the study, 75 – 86% of orlistat users took a MVI and about 80% of MVI users took the MVI at least once a day. However only 38 – 53% of study participants interviewed timed the MVI correctly with their orlistat.

Reviewer comments:

1. *The reason for noncompliance with MVI use as directed is unclear. The communication on the orlistat label may not be understood by consumers or consumers may be confused by instructions for use on the MVI label that conflict with the MVI instructions for use on the orlistat label. The orlistat labeling does not inform consumers that the MVI label may contain instructions for use different than that recommended when used with orlistat.*

2. *The percentage of subjects timing the MVI correctly with orlistat increased during the course of the study. It is not clear whether more compliant individuals remained in the study longer or whether subjects learned from repeated questions about MVI use during the CATI interview.*

The orlistat label used for the actual use study placed the MVI instruction under *Other Information* at the end of Drug Facts. The label submitted with NDA 21-887 moved the information about taking a MVI into the *Directions* section. The proposed Drug Facts label for orlistat OTC does not contain information that orlistat decreases the absorption of fat-soluble vitamins and beta-carotene, nor does it explain that this is why it is important to correctly take a

MVI when using orlistat. The patient package insert for Xenical (orlistat, 120 mg) includes the following question and answer:

> ***Should I take a multivitamin with Xenical?***
> *Xenical interferes with your body's absorption of some fat-soluble vitamins. Therefore, when you use Xenical, you should take a daily multivitamin supplement that contains vitamins D, E, K, and beta-carotene. Take your multivitamin once a day at least 2 hours before or after taking Xenical, such as at bedtime.*

Reviewer comments:

1. *Orlistat OTC proposed labeling limits the duration of use to six months, but consumers may take repeated courses of orlistat or may continue use beyond the labeled six month period. Over time, fat-soluble vitamin deficiencies could occur in susceptible individuals who do not take a properly timed, daily MVI while using orlistat.*

2. *Results from the label comprehension study may demonstrate consumer understanding of the vitamin information in the **Directions** section of the Drug Facts label. If not, it may be important to explore other ways to increase consumer compliance with correct orlistat/MVI dosing.*

Use of educational materials and compliance with dietary recommendations
As shown in Table 17, the supplementary educational materials were utilized to varying degrees and with varying frequency among study subjects. However, 77 – 86% of subjects found each of the five evaluated materials useful. The diet success planner was used the least often and was found to be the least useful of the five materials. The fat counter was used the most often by the most subjects. The fat counter and the *How to Lose Weight with Orlistat* booklet were perceived as most useful. These materials were prepared by Roche, and GSKHC does not state whether or not these educational materials were tested for comprehension prior to use in the actual use study. The sponsor did not compare subjects' weight loss during the study with use of the educational materials. In addition to the written educational materials, subjects had access to educational information on a website. Only 13% of subjects used the website and about half found it useful.

When GSKHC submitted NDA 21-887, they submitted newly designed educational materials that closely parallel the information offered with the Roche materials. The label comprehension study review will discuss comprehension of the labeling submitted to NDA 21-887.

Table 17: Summary of frequency of use and perceived usefulness of educational materials among users (final interview, N = 156)					
Educational material	Subjects Used (%)	Frequency of use (%)		Perceived usefulness (%)	
		Often or Sometimes	Rarely or never	useful	Not useful
Diet success planner	30.8%	37.5	62.5	77.1	20.9
Fat wheel	46.2%	58.3	41.7	79.1	18.1
Fat counter	64.1%	70.0	29.0	86.0	12.0
How to lose weight with orlistat	41.7%	47.7	50.8	84.6	15.4
Personal food diary	42.3%	66.7	33.3	80.3	18.2

During the course of this study, the number of subjects following any kind of diet declined from 80% at the Day 14 interview to 61% at the Day 90 interview. Of those following a diet, 65 – 77% of subjects followed a reduced fat diet, and 35 – 43% of subjects used a reduced calorie diet. Between 93 and 98% of subjects claimed at least some success in maintaining their diet. At the final interview, 73% of subjects believed that orlistat helped them lose weight. Tables 18 and 19 summarize this data. Subject information on kind of diet and success in maintaining diet was obtained through the follow-up telephone interviews. Although subjects had a place to record dietary intake in the subject diaries, the structured interview did not ask subjects to refer to the information in their diaries. On request for further information, the sponsor stated that subject diaries were an educational tool and were not reviewed or collected during the study.

Table 18: Summary of Subjects' Dietary Behavior During Study				
Parameter	**Interview data**			
	Day 14 (N = 217)	**Day 30 (N = 219)**	**Day 60 (N = 197)**	**Day 90 (N = 148)**
Following any kind of diet				
Yes	173 (79.7%)	151 (68.9%)	114 (57.9%)	90 (60.8%)
No	43 (19.8%)	66 (30.1%)	80 (40.6%)	55 (37.2%)
Missing or No answer	1 (0.5%)	2 (0.9%)	3 (1.5%)	3 (2.0%)
Kind of diet				
Reduced calorie	75 (43.4%)	61 (40.4%)	38 (33.3%)	32 (35.6%)
Reduced fat	134 (77.5%)	115 (76.2%)	80 (70.2%)	59 (65.6%)
Fat free	1 (0.6%)	3 (2.0%)	3 (2.6%)	0
Reduced carbohydrate	51 (29.5%)	30 (19.9%)	20 (17.5%)	21 (23.3%)
Reduced protein	1 (0.6%)	2 (1.3%)	0	1 (1.1%)
Other	23 (13.3%)	31 (20.5%)	26 (22.8%)	21 (23.3%)
Success in maintaining diet				
Not successful	7 (4.0%)	6 (4.0%)	2 (1.8%)	3 (3.3%)
Somewhat successful	94 (54.3%)	88 (58.3%)	70 (61.4%)	48 (53.3%)
Very successful	71 (41.0%)	57 (37.7%)	42 (36.8%)	39 (43.3%)
No answer	1 (0.6%)	0	0	0

Overall, the percentage of patients following any type of diet declined from a high of 79.7% around study day 14 to 68.9% around study day 30, and down to 60.8% around study day 90.

Reviewer comment:

1. *The variation in the percentages of subjects using different types of diets during the study may reflect subjects changing their dietary intake or may reflect differences between the cohort of subjects who continued the study and those who discontinued the study at any particular time point.*

Table 19: Subject perception at final interview (N = 198): Did orlistat help you lose weight?

Yes (73.2%)	No (23.7%)
Why was orlistat effective in helping you lose weight?	Why was orlistat not effective in helping you lose weight?
Effective product (inhibits fat absorption) (49.7%) Helped modify eating habits/eating awareness (43.4%) Improved bowel regularity (3.4%) Other (14.5%)	Product not effective (29.8%) Don't know (19.1%) Did not use correctly (12.8%) Didn't exercise (10.6%) Diet issues (10.6%) Adverse side effects (8.5%) Did not use product long enough (8.5%) Health issues (6.4%) Other (8.5%)

More than 73% of study subjects thought that orlistat helped them lose weight. Forty-three percent of these subjects felt that their success was due to orlistat helping them with dietary modifications and a heightened awareness of eating habits. The sponsor did not offer data to determine whether subjects relied on the educational materials to support these behavioral changes and whether they used adverse event severity as a gauge for dietary compliance.

Prior to the study, subjects, who used study medication, reported exercising 0 – 20 times per week, with a mean of 2.6 times per week. During the study, subjects reported exercising 0 – 21 times per week, with a mean of 3.1 – 3.3 times per week.

Weight loss efficacy

During this three month actual use study, maximum mean weight loss by self-reported weight occurred at the Day 90 interview. At that time, 80% of subjects had lost at least 5 pounds and 49% had lost more than 5% of their body weight. According to the sponsor, the mean weight loss overall was 10.6 pounds (4.8 kg) by self-report and 7.2 pounds (3.3 kg) by measured weight. At the time of the final telephone interview, at least 14 days after stopping orlistat, some weight regain had occurred by self report.

Tables 20 and 21 display detailed data about the mean weight loss and percent body weight loss at various study assessment intervals and the relationship between starting BMI and weight loss during the study. Individuals with higher baseline BMIs lost more weight on average. It is not clear whether percent body weight lost or change in BMI differed with baseline BMI. At the end of the 90 day study, nearly 41% of subjects achieved more than a 5% decrease in body weight (by self-reported weights). All subjects in the user population were reached for the final follow-up telephone interview.

During the study, only 15.6 – 32.5% of subjects were weighed at the pharmacy during each 30-day study interval. Only 25% of the user population had a measured weight done between study days 60 and 90. Among these subjects, 41.6% had lost more than 5% of their baseline body weight. There are no objective weight measurements for the other 75% of study drug users during the last 30 days of the study and there is no objective weight performed at the conclusion of the study. In Table 18, the data in the *Last MW* column is not interpretable, as it reflects mean weight changes based on subjects' last measured weights regardless of when the measurement occurred during the study. Although subjects were instructed to return to the pharmacy at the end of their study participation, only 44.7% of purchasers (109 of 237 subjects) participated in a final pharmacy visit and weight measurement. It is not possible to evaluate weight loss maintenance beyond three months nor is it possible to determine whether weight loss would have continued through a six month treatment period in the actual use setting.

Table 20: Integrated table of self-reported (SRW) and measured weight (MW) loss during actual use study

		% subjects with weight loss at interviews and pharmacy visits								
		Day 14 SRW (N = 217)	Day 1-30 MW (N = 37)	Day 30 SRW (N = 219)	Day 31-60 MW (N = 77)	Day 60 SRW (N = 197)	Day > 60 MW (N = 60)	Day 90 SRW (N = 148)	Last MW (N = 106)	Final SRW (N = 237)
Weight lost (pounds)	> 5	20.4%	32.4%	40.9%	42.9%	65.2%	55.0%	79.9%	51.0%	69.9%
	> 10	3.1%	10.8%	7.4%	15.6%	26.2%	38.3%	41.8%	24.6%	34.7%
	> 15	0	8.1%	1.8%	5.2%	9.7%	23.3%	20.2%	14.2%	16.6%
	> 20	0	2.7%	0.6%	1.3%	3.0%	15.0%	12.0%	9.5%	9.3%
	> 25	0	0	0.6%	0	2.4%	6.7%	4.5%	3.8%	3.6%
	missing	7.1%	10.8%	8.7%	1.3%	6.1%	10.0%	2.2%	0	3.6%
% body weight lost	> 0 – 5%	92.9%	81.1%	91.3%	80.5%	94.0%	74.9%	97.6%	82.1%	96.2%
	> 5%	4.1%	13.5%	13.0%	18.2%	33.6%	41.6%	49.1%	28.3%	40.8%
	> 10%	0	0	0.6%	1.3%	4.9%	8.3%	14.8%	4.7%	11.3%
	> 15%	0	0	0	0	1.2%	5.0%	1.4%	2.8%	1.5%
	> 20%	0	0	0	0	0.6%	0	0.7%	0	1.0%
	missing	7.1%	10.8%	8.7%	1.3%	6.1%	10.0%	2.2%	0	3.6%

The data in Table 21 demonstrate a positive correlation between starting BMI and mean self-reported and measured weight loss at the end of the actual use study. The range of weight loss shows that some subjects had a net weight gain during the study regardless of starting BMI. More detailed information has been requested, but not yet received, from GSKHC regarding subjects who gained weight during the study.

Among the ten low literate subjects who used orlistat, all lost weight by self-report. Two subjects used orlistat for only 9 or 12 days and lost 1.0% and 2.3% of their body weight respectively. The other eight low literate subjects used orlistat for 53 – 90 days and reported losing 2.4 – 11.4% body weight. Only three subjects (30%) lost 5% body weight or more. Five of these subjects had a last pharmacy visit and an objective weight measurement. One of these subjects had gained six pounds (3.8% body weight gain) and another lost only one pound. Two morbidly obese subjects lost more weight than documented by self-report (10.4% and 19.7% body weight loss).

Upon request, the sponsor provided information about weight loss among the 21 orlistat users who were excluded from the analysis due to protocol violations at one of the pharmacy sites. Despite protocol requirements for at least one follow-up pharmacy visit, the 21 subjects completed only 4 pharmacy visits during the study: one between Days 1 – 30, one between Day 60 – 90, and two last return visits at the end of study participation. These subjects experienced a mean weight loss of 4.5 pounds (2.0 kg). By self-reported weights at the final interview, 17 of 21 subjects reported a mean weight loss of 9.8 pounds (4.5 kg). The mean self-reported weight loss for this group of subjects was similar to the overall mean weight loss for the analysed orlistat user population which lost 10.6 pounds (4.8 kg).

Table 21: Relationship between self-reported (SRW) and measured weight (MW) loss in pounds and baseline BMI*

Baseline BMI (kg/m^2)	Number of subjects		Median weight loss (lbs)		Mean weight loss (lbs)± SD		Range of weight loss (lbs)	
	SRW	MW	SRW	MW	SRW	MW	SRW	MW
< 25	12	6	5.0	1.5	6.1 ± 4.9	2.0 ± 3.9	2 to 20	-3 to 7
25 – 29.9	57	28	7.0	4.5	8.0 ± 4.8	5.1 ± 5.0	2 to 24	-6 to 19
≥ 30	117	72	10.0	6.5	12.3 ± 8.2	8.4 ± 11.0	2 to 45	-8 to 52
Total	186	106	9.0	6.0	10.6 ± 7.5	7.2 ± 9.6	2 to 45	-8 to 52

* Pearson correlation coefficient between self-reported weight loss and baseline BMI = 0.23, with p = 0.002. Pearson correlation coefficient between the measured weight loss and the baseline BMI = 0.22 with p = 0.024.

Table 22 displays a comparison between mean weight loss data from this actual use study and mean weight loss data from some of the placebo-controlled, randomized studies conducted with orlistat (BM14149, BM 14150, NM17247 – see Appendix 10.5). The three placebo-controlled trials all continued longer than 90 days, and the BM14149 and BM 14150 studies had 12 month active weight loss treatment phases followed by 12 month maintenance weight loss phases. All studies had a treatment arm with orlistat 60 mg.

Table 22: Comparison of weight loss achieved with orlistat 60 mg and placebo (if done) from studies NM17285, NM17247, BM14149, and BM14150

Weight parameter	NM17285	NM17247	BM14149*	BM14150*
Mean % body weight change at 13 weeks on orlistat 60 mg	Estimated at < -5%	-2.9% (ITT)	-6.2% (ITT)	-7.4% (ITT)
Mean % body weight change at 13 weeks on placebo	-	-1.9% (ITT)		
Mean weight loss on orlistat 60 mg	At 90 days: 3.3 – 4.8 kg	At 85 days: 2.8 kg	At 365 days: 4.6 kg (ITT)	At 168 days: 1.9 kg (ITT)
Mean weight loss on placebo			At 365 days: 2.5 kg	

Reviewer comment:

1. *Best estimates of weight loss during the actual use study (NM17285) are derived from the subjective and objective data and appear similar to the data from study NM17247. The difference between % body weight change between the placebo and orlistat 60 mg treatment groups in NM17247 is only 1%. The BM14149 and BM14150 studies both provided active dietary counseling and recruited an obese population. The greater weight loss noted in these studies at 13 weeks may be due to: a subject population with higher starting BMIs, differences in dietary and medical support during the trial, or other unidentified factors.*

6.1.5 Clinical Microbiology

Not applicable as the proposed product is not an antimicrobial.

6.1.6 Efficacy Conclusions

- During this actual use study, subjects appeared to lose some weight using orlistat 60 mg up to TID and the supportive educational materials provided. However, due to the lack of objective subject weight assessments, it is not possible to make evidence-based conclusions regarding weight loss achieved during the actual use study. Objective weight measurements were obtained in only 15 – 33% of subjects at any one assessment interval during the study, and no objective weight measurement was taken at the end of the study.

- It is not possible to distinguish between weight loss achieved through use of the supplemental educational materials versus weight loss achieved with the use of these materials and orlistat, 60 mg, although subjective data collected through telephone interviews suggest that consumers found the accompanying educational materials to be generally helpful.

- According to subject reporting during telephone interviews, subjects took an appropriate number of orlistat capsules per dose and took an appropriate total daily dose. However, there are no objective data to support this conclusion.

- Although the actual use study began with 703 eligible subjects, only 237 of these subjects became orlistat users. This population may be too small and not diverse enough to accurately reflect consumer behavior decisions and weight loss patterns among American consumers likely to use this product. The study population underrepresented individuals of low literacy and those of non-Caucasian ethnicity.

- Some misuse of orlistat occurred during the actual use trial. While all male subjects were overweight by BMI criteria, 8.9% of female subjects were not overweight. None of the study subjects were underweight, although two subjects perceived themselves as underweight. It is possible that similar misuse of orlistat may occur with OTC marketing.

- Subject self-selection decisions suggest either a problem with label comprehension or extensive disregard for label warnings. Even if self-selection and use decisions are examined for only the labeled exclusions that remain on the proposed NDA label, correct self selection and use decisions by subjects ranged between 0 – 50% for unconditional exclusions and 12.1 – 50.0% for conditional exclusions. The sponsor does not provide data to confirm whether subjects with conditional exclusions actually consulted their healthcare professionals or data about the reasons consumers disregarded label warnings.

- This study does not demonstrate consumer use decisions beyond 90 days of drug use. There is no data to support labeling for six-month duration of use for this product. Results from placebo-controlled orlistat studies of longer duration suggest that weight loss continues beyond three months of use; however, the decrease in adherence to diet seen during this three month study suggests that weight loss might plateau, especially with the lack of a learned intermediary to reinforce lifestyle changes. It is not possible to determine consumer usage patterns during the fourth to sixth months of orlistat use. It would be helpful to understand what percentage of consumers would continue orlistat beyond a labeled three- or six-month treatment duration.

- During the first two weeks of the study, nearly 80% of subjects reported following some type of diet. However, the number of subjects using orlistat and following a diet plan declined during the study to about 60% by study's end. Among subjects who followed a diet, most reported using a low-fat and/or reduced calorie diet. There are no data provided that illustrate food choices and serving sizes consistent with these diets. There are no data demonstrating that subjects understood the differences between different types of diets.

7 INTEGRATED REVIEW OF SAFETY

The integrated review of safety is contained in the medical officer review by Julie Golden, M.D. from the Division of Metabolism and Endocrinologic Products. This review evaluates the safety data from the actual use study and compares the adverse event profile to that seen in previously conducted randomized, placebo-controlled trials that studied orlistat 60 mg.

7.1 Methods and Findings

As suggested above, the sections of the safety review will address safety as it relates to the actual use study data.

7.1.1 Deaths

No deaths occurred in the orlistat OTC development program for weight loss in overweight adults or for treatment of obesity and obesity management.

Nine deaths occurred during a four year orlistat study in a Swedish population of obese male and female subjects with normal or impaired glucose tolerance. The study was designed to evaluate whether orlistat 120 mg TID could prevent or delay the development of type 2 diabetes compared to placebo. Seven deaths occurred in the placebo group and two in the orlistat group. Two more placebo patients died after finishing study participation. One 45-year old male subject randomized to orlistat completed 82 study days and then committed suicide on Day 84. The other death in a subject randomized to orlistat occurred in a 53 year old male who experienced a

myocardial infarction on study day 503. Four deaths due to myocardial infarction occurred in the placebo group between study day 397 and study day 1060. This information was obtained from the medical officer review by Eric Colman, M.D. dated 10/21/2004 in DFS.

Office of Drug Safety Postmarketing Safety Reviews from September 2003 and July 2004 found two fatal U.S. cases associated with the use of orlistat. A 54-year old woman was using orlistat for four months when she developed abdominal burning and pain. She was diagnosed with a metastatic pelvic cancer of unknown primary source involving ovary, colon, and other pelvic structures. She died two months later. The second possible case was reported by a female consumer who heard that a 29-year old woman on orlistat died recently from cardiac arrest. No further details were available.

7.1.2 Other Serious Adverse Events

During the actual use study, five subjects experienced six adverse events considered serious. These events are listed in Table 23. Among these AEs, the abdominal pain and chest pain were classified as possibly related to study drug. The other four events were considered unrelated to orlistat use.

Table 23: Serious adverse events: 6 events among 5 subjects

Adverse event	Subjects N (%)
Kidney infection NOS	1 (0.4%)
MRSA* infection	1 (0.4%)
Abdominal pain NOS	1 (0.4%)
Chest pain NEC	1 (0.4%)
Abortion, spontaneous	1 (0.4%)
Transient ischemic attack	1 (0.4%)
Total	5 (1.8%)

*methicillin-resistant staphylococcus aureus

A detailed description of these serious adverse event cases was provided by the sponsor and is reproduced below.

1. Subject 11015:
   The subject was a 46-year old Black female who developed severe nausea and vomiting and "terrible stabbing" abdominal pain bilaterally under her rib cage with radiation into her back on June 19, 2003. She was evaluated in an emergency department and then was admitted to the hospital. She had a history of gastroesophageal reflux disease and anemia (8 years, on iron). The subject did not allow release of her medical records.

   She received IV Demerol and an IV anti-emetic, which relieved the nausea and vomiting. Multiple tests were done that included: EKG, urinalysis, stool for occult blood, blood tests, CT scan of abdomen, and an abdominal ultrasound. All tests were negative except for a low

hematocrit, for which the physician recommended transfusion. The subject refused transfusion and was released from the hospital on June 20, 2003, with a prescription for Prevacid, which she did not fill. Her abdominal pain resolved on June 24, 2003.

Orlistat was started on May 20, 2003 (60 mg TID), with usage interrupted from June 19 – June 21, 2003. The medical reviewer thought that there was possible causality between the event and the study drug.

2. Subject 11052:
The subject was a 48-year old Caucasian female who developed severe, crushing pain, with radiation of the pain into her left arm on August 1, 2003. No information concerning her past medical history was available because she did not allow release of her medical records. She was seen in an emergency department (ED) where multiple testing was done including: cardiac MRI, EKG (sinus arrhythmia – normal variant), stress test, and cardiac enzymes. All tests were within normal limits. She received nitroglycerin. Her pain resolved, and she was released from the emergency department after ten hours with a diagnosis of esophageal spasm. She was discharged with prescriptions for Nexium and hyoscyamine, which she started on August 2, 2003. She had two more episodes of pain after leaving the ED. Both episodes were relieved with hyoscyamine.

The subject started using orlistat on June 25, 2003 (60 mg TID) and stopped on August 1, 2003. The event was judged to have possible causality to the study drug.

3. Subject 13017:
This subject was a 60-year old Caucasian female who was diagnosed with a urinary tract infection (UTI) on June 13, 2003, and took Bactrim until June 23, 2003. Symptoms of lower back pain and urinary frequency worsened on June 23, 2003, and the subject developed nausea and fever was admitted to the hospital with a diagnosis of pyelonephritis. The subject had a history of UTIs and kidney infections. Laboratory findings included an elevated serum white blood cell (WBC) count and a urinalysis with elevated WBCs and bacteria. The subject was treated with IV ciprofloxacin for two days followed by oral ciprofloxacin for one week. She was discharged from the hospital on June 25, 2003.

Orlistat was started on June 12, 2003 (60 mg TID) and stopped June 14, 2003. The subject planned to restart the orlistat on July 30, 2003. The event was judged unrelated to study drug.

4. Subject 28040:
The subject was a 55-year old female who collapsed on August 19, 2003, and was taken to an ED. She was admitted to the hospital to rule out a transient ischemic attack (TIA). She had a past history of adrenal gland failure, high cholesterol, blood clots, asthma, GERD, hypothyroidism, osteoarthritis, depression, and hypertension. While in the hospital, she had the following assessments: MRI (brain), MRI (knee), radiographs of chest and lumbar spine, renal and carotid ultrasounds, laboratory tests including anti-nuclear antibody (ANA) test.

Abnormal results included: a positive ANA, osteoarthritis of the knee, and degenerative and postoperative changes in the lumbar spine and chest.

She was treated with IV potassium and other electrolytes while hospitalized. She was discharged on August 27, 2003, with a diagnosis of syncope and a prescription for potassium.

Orlistat was started on June 6, 2003 (60 mg TID), and was stopped on August 18, 2003. the subject planned to restart the study drug once recovered. This event was judged unrelated to study drug.

5. Subject 28040:
   This is the second serious adverse event reported for this subject. After her admission to the hospital, the subject was diagnosed with MRSA (methicillin-resistant staphylococcus aureus) of her urine. This diagnosis prolonged her hospital stay. Of significance is the past history of back surgery with postoperative MRSA infection of the wound. While in the hospital, a urinalysis (elevated white blood cell count, positive leukocytes and bacteria) and urine culture (positive for MRSA) were done. She had a bladder catheter placed and received IV vancomycin. She was released from the hospital with a prescription for Fludrocort, rifampin, and doxycycline.

   Orlistat was started on June 6, 2003 (used 60 mg, twice daily). She stopped using it on August 18, 2003, the day before the SAE occurred. She reported plans to restart the drug when she recovered. The event was judged unrelated to the study drug.

6. Subject Number 16002:
   The subject was a 19 year old Caucasian female who reported being pregnant during her last interview. She stated that her physician saw her on June 23, 2003, for nausea and vomiting. At that time, a pregnancy test was done and was positive. Her past medical history included a Wilm's tumor with a subsequent nephrectomy at seven months of age, depression, and bipolar disorder. Prior to being pregnant, the subject had been using Depo-Provera injections for birth control for two years and did not have a menstrual period during that time. Her estimated date of delivery was January 7, 2004. On February 4, 2004, the subject was contacted, and she said that she had a miscarriage in September 2003. She refused to give any other information.

   Orlistat was started on May 29, 2003. She used 60 mg three times a day and occasionally doubled the dosage. She stated she would take fewer capsules if she were eating a lower fat meal. She stopped the study medicine on June 23, 2003. The event was judged unrelated to study drug.

Reviewer comment:

1. *Based on her estimated date of delivery (which was most likely determined by ultrasound), subject 16002 started taking orlistat at 8 weeks gestational age and stopped taking it prior to 12 weeks gestation. By her report, the pregnancy ended between 22 and 26 weeks gestation, which technically is not a spontaneous abortion. The subject refused*

to release further information, so it is impossible to know whether the pregnancy ended due to fetal demise in-utero, preterm labor and delivery with or without preterm premature rupture of membranes, or other reasons. The subject may have had a voluntary pregnancy termination and chosen not to share this information with study personnel. In addition, there is no information about concomitant medications used to treat her bipolar disorder and depression. Based on the limited information available, it is likely that the orlistat was not related to the pregnancy outcome.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The sponsor did not provide specific demographic or weight loss information on subjects who dropped out of the study. Information was provided on adverse events associated with study discontinuation.

7.1.3.1 Adverse events associated with dropouts

A total of 43 subjects (15.8% of user population) discontinued orlistat treatment due to adverse events. Table 24 lists each adverse event leading to discontinuation and its incidence. The number of severe adverse events is provided for each listing. All adverse events occurring in at least 1% of discontinuing subjects involved gastrointestinal symptoms.

Table 24: AEs that led to discontinuation from the study

Adverse event	Orlistat use discontinued N(%)	Subjects with severe AE
Gastrointestinal AEs		
Flatulence	8 (2.8%)	2
Fecal incontinence	5 (1.8%)	1
Fecal urgency	5 (1.8%)	0
Liquid stools	5 (1.8%)	2
Abdominal pain NOS	4 (1.4%)	1
Decreased defecation	3 (1.1%)	1
Flatus with discharge	3 (1.1%)	0
Oily evacuation	3 (1.1%)	0
Oily spotting	3 (1.1%)	0
Soft stools	3 (1.1%)	0
Abdominal pain upper	2 (0.7%)	0
Increased defecation	2 (0.7%)	0
Vomiting NOS	2 (0.7%)	0
Diarrhea NOS	1 (0.4%)	1
Frequent bowel movements	1 (0.4%)	0
Hemorrhoids	1 (0.4%)	0
Nausea	1 (0.4%)	1
Esophageal reflux	1 (0.4%)	0

(continued on next page)

Table 24: AEs that led to discontinuation from the study		
Adverse event	**Orlistat use discontinued N(%)**	**Subjects with severe AE**
(continued from previous page)		
Non-gastrointestinal AEs		
Gastroenteritis viral NOS	3 (1.1%)	1
Upper respiratory tract infection NOS	1 (0.4%)	0
Chest pain NEC	1 (0.4%)	1
Fatigue	1 (0.4%)	0
Hypertension NOS	2 (0.7%)	1
Back injury NOS	1 (0.4%)	0
Cardiovascular function test abnormal	1 (0.4%)	0
Carpal tunnel syndrome	1 (0.4%)	0
Periorbital edema	1 (0.4%)	0

Table 25 summarizes the actions taken by subjects in response to defecation pattern adverse events experienced while taking orlistat. Subjects reported one action for each adverse event experienced. Most adverse event data was collected through the CATI telephone interview process. If the adverse experience was reported more than once, the subject may have taken the same action or a different action with another occurrence of the same adverse event. It is not clear whether the sponsor only included permanently discontinued subjects in the *use discontinued* column or if some of those subjects resumed study drug use at some time after reporting discontinuation.

Table 25: Actions taken by subjects in response to changes in defecation pattern AEs				
Defecation pattern change	**Subjects N (%)**	**Action taken**		
		Continued use	**Orlistat use interrupted**	**Orlistat use discontinued**
Oily spotting	38 (13.4%)	31 (81.6%)	4 (10.5%)	3 (7.9%)
Fecal urgency	36 (12.7%)	26 (72.2%)	5 (13.9%)	5 (13.9%)
Liquid stools	31 (10.9%)	17 (54.8%)	9 (29.0%)	5 (16.1%)
Flatus with discharge	30 (10.6%)	22 (73.3%)	5 (16.7%)	3 (10.0)
Fecal incontinence	23 (8.1%)	15 (65.2%)	3 (13.0%)	5 (21.7%)
Fatty/oily stool	20 (7.0%)	18 (90.0%)	2 (10.0%)	0
Oily evacuation	20 (7.0%)	14 (70.0%)	3 (15.0%)	3 (15.0%)
Increased defecation	15 (5.3%)	10 (66.7%)	3 (20.0%)	2 (13.3%)
Decreased defecation	14 (4.9%)	10 (71.4%)	1 (7.1%)	3 (21.4%)
Soft stools	12 (4.2%)	9 (75.0%)	0	3 (25.0%)
Total	136 (47.9%)	89 (65.4%)	23 (16.9%)	24 (17.6%)

7.1.3.2 Other significant adverse events

There were no other significant adverse events.

7.1.4 Other Search Strategies

Not applicable

7.1.5 Common Adverse Events

Table 26 displays the common adverse events (total and treatment related) experienced by subjects at least 1% of actual use study subjects. As expected from orlistat's mechanism of action and consistent with data from other orlistat studies, gastrointestinal disorders occurred most often and the majority of events were mild to moderate in severity.

Table 26: Summary of adverse event frequency and severity for adverse events occurring in ≥1% of study subjects.

Adverse Events by Body System	Subjects N (%)	# events by severity			Subjects with treatment-related AE
		Mild	Moderate	Severe	
Gastrointestinal disorders	168 (59.2%)	324	143	26	
Abdominal pain NOS	43 (15.1%)	44	11	4	39 (13.7%)
Oily spotting	38 (13.4%)	34	16	2	38 (13.4%)
Fecal urgency	36 (12.7%)	35	14	2	36 (12.7%)
Flatulence	36 (12.7%)	35	11	2	35 (12.3%)
Liquid stools	31 (10.9%)	26	13	5	30 (10.6%)
Flatus with discharge	30 (10.6%)	24	14	1	30 (10.6%)
Fecal incontinence	23 (8.1%)	12	17	4	23 (8.1%)
Ratty/oily stool	20 (7.0%)	21	5	0	20 (7.0%)
Oily evacuation	20 (7.0%)	20	7	0	20 (7.0%)
Increased defecation	15 (5.3%)	9	9	1	15 (5.3%)
Decreased defecation	14 (4.9%)	14	2	1	13 (4.6%)
Soft stools	12 (4.2%)	9	5	0	12 (4.2%)
Nausea	11 (3.9%)	7	3	1	7 (2.5%)
Abdominal distension	10 (3.5%)	9	1	0	9 (3.2%)
Abdominal pain upper	10 (3.5%)	6	3	2	10 (3.5%)
Dyspepsia	5 (1.8%)	5	1	0	5 (1.8%)
Constipation	4 (1.4%)	3	1	0	3 (1.1%)
Hemorrhoids	4 (1.4%)	2	2	0	4 (1.4%)
Frequent bowel movements	3 (1.1%)	1	2	0	2 (0.7%)
Vomiting NOS	3 (1.1%)	2	1	0	2 (0.7%)
Other					
Influenza	7 (2.5%)	2	4	1	
Ear infection NOS	6 (2.1%)	4	2	0	
Gastroenteritis viral NOS	5 (1.8%)	0	2	3	
Nasopharyngitis streptococcal	5 (1.8%)	4	1	0	
Sinusitis NOS	5 (1.8%)	1	4	0	
Upper respiratory infection	5 (1.8%)	3	2	0	
Bladder infection NOS	4 (1.4%)	2	2	0	
Bronchitis NOS	3 (1.1%)	1	2	0	

(continued on next page)

Table 26: Summary of adverse event frequency and severity for adverse events occurring in ≥1% of study subjects.					
Adverse Events by Body System	Subjects N (%)	# events by severity			Subjects with treatment-related AE
		Mild	Moderate	Severe	
(continued from previous page)					
Headache NOS	16 (5.6%)	13	10	0	6 (2.1%)
Migraine NOS	4 (1.4%)	0	4	3	
Arthralgia	5 (1.8%)	1	2	2	
Muscle cramps	4 (1.4%)	3	1	0	4 (1.4%)
Back pain	3 (1.1%)	2	1	0	
Fatigue	8 (2.8%)	5	4	0	7 (2.5%)
Pain NOS	5 (1.8%)	3	2	0	
Chest pain NEC	4 (1.4%)	2	2	1	3 (1.1%)
Rhinitis, seasonal	4 (1.4%)	4	0	0	
Allergy aggravated	4 (1.4%)	4	0	0	
Hypertension NOS	5 (1.8%)	3	1	2	
Blood cholesterol increased	3 (1.1%0	3	0	0	

Table 27 illustrates the similar incidences of various adverse events across orlistat studies of various durations and populations. Studies BM14149 and BM14150 were conducted in obese populations, whereas study NM17247 was conducted in an overweight population, and study NM17285 was conducted in an actual use setting.

Table 27: Comparison of adverse events across orlistat studies							
Study subjects (%) / Body system/ Adverse event	**NM17285**	**NM17247 (data at 4 mths)**		**BM14149 (data at one year)**		**BM14150 (data at one year)**	
	Orlistat 60 mg	Placebo	Orlistat 60 mg	Placebo	Orlistat 60 mg	Placebo	Orlistat 60 mg
Gastrointestinal Disorders	59.2%	33%	57%	52.7%	63.2%	46%	75.6%
Abdominal pain	15.1%	3%	4%	11.8%	15.5%	13.7%	16.3%
Oily spotting	13.4%	0	11%	0.8%	12.6%	0	14.6%
Fecal urgency	12.7%	6%	17%	5.1%	10.0%	1.6%	8.1%
Flatulence	12.7%	11%	7%	4.2%	5.0%	3.2%	9.8%
Liquid stools	10.9%	3%	3%	10.1%	14.6%	12.1%	19.5%
Flatus with discharge	10.6%	2%	9%	0.8%	6.3%	0	6.5%
Fecal incontinence	8.1%	0	3%	1.3%	2.5%	0	3.3%
Fatty/oily stool	7.0%	3%	22%	4.2%	20.5%	2.4%	20.5%
Oily evacuation	7.0%	< 1%	3%	0.4%	3.8%	0	5.7%
Increased defecation	5.3%	4%	9%	3.0%	7.5%	5.6%	18.7%
Decreased defecation	4.9%	7%	5%	7.2%	2.9%	12.9%	10.6%
Soft stools	4.2%	4%	6%	8.4%	14.6%	8.1%	18.7%
Nausea	3.9%	4%	3%	3.0%	2.9%	5.6%	7.3%
Abdominal distension/ discomfort	3.5%	6%	2%	1.7%	1.7%		
(continued on next page)							

Table 27: Comparison of adverse events across orlistat studies

Study subjects (%) / Body system/ Adverse event	NM17285	NM17247 (data at 4 mths)		BM14149 (data at one year)		BM14150 (data at one year)	
	Orlistat 60 mg	Placebo	Orlistat 60 mg	Placebo	Orlistat 60 mg	Placebo	Orlistat 60 mg
(continued from previous page)							
Abdominal pain, upper	3.5%	3%	3%	-	-		
Dyspepsia	1.8%	0	3%	0.8%	0.8%		
Constipation	1.4%	-	-	-	-		
Hemorrhoids	1.4%	0	1%	1.7%	1.3%	0	0
Frequent bowel movements	1.1%	0	< 1%	-	-		
Vomiting	1.1%	2%	2%	3.8%	1.3%	3.2%	2.4%
Infections and infestations	14.4%	14%	21%				
Influenza	2.5%	2%	0				
Gastroenteritis, viral	2.1%	2%	0				
Nasopharyngitis	1.8%	3%	3%				
Sinusitis	1.8%	2	4%				
Upper respiratory tract Infection	1.8%	3%	6%				
Bladder infection	1.4%	2%	< 1%				
Bronchitis	1.1%	< 1%	3%				
Nervous system disorders	10.2%	8%	7%	32.5%	30.1%		
Headache	5.6%	3%	5%				
Migraine	1.4%	3%	< 1%				
Musculoskeletal, connective Tissue, and bone disorders	8.1%	6%	7%	43.5%	35.6%		
Arthralgia	1.8%	< 1%	1%				
Muscle cramps/myalgia	1.4%	2%	3%				
Back pain	1.1%	1%	1%				
General disorders and Administration site conditions	6.7%	2%	2%	19.8%	16.3%		
Fatigue/lethargy	2.8%	< 1%	0				
Pain	1.8%	0	< 1%				
Injury /poisoning	4.6%	2%	4%				
Respiratory, thoracic, and Mediastinal disorders	3.2%	4%	3%	40.5%	31.4%		
Rhinitis, seasonal	1.4%	0	< 1%				
Renal and urinary Disorders	2.5%	1%	0	12.7%	15.5%		
Immune system disorders	2.1%	0%	< 1%	47.3%	47.3%		
Allergy aggravated	1.4%	0%	< 1%				
(continued on next page)							

Table 27: Comparison of adverse events across orlistat studies							
Study subjects (%) / Body system/ Adverse event	**NM17285**	**NM17247 (data at 4 mths)**		**BM14149 (data at one year)**		**BM14150 (data at one year)**	
	Orlistat 60 mg	Placebo	Orlistat 60 mg	Placebo	Orlistat 60 mg	Placebo	Orlistat 60 mg
(continued from previous page)							
Skin and subcutaneous Tissue disorders	2.1%	5%	3%	19.8%	14.6%		
Vascular disorders	2.1%	< 1%	< 1%	3.4%	2.1%	0.8%	0
Hypertension	1.8%						
Investigations	1.8%	0	< 1%				
Blood cholesterol increased	1.1%						
Neoplasms, benign and malignant	1.1%	0	1%	0	0		
Cardiac disorders	0.7%	< 1%	< 1%	7.2%	5.9%		
Psychiatric disorders	0.7%	3%	2%	8.0%	5.9%		
Reproductive system and Breast disorders	0.7%	1%	3%	15.6%	12.1%		
Ear and labyrinth disorders	0.4%	< 1%	0	6.3%	4.6%		
Endocrine disorders	0.4%	-	-	1.3%	0.8%	0.8%	0
Eye disorders	0.4%	2%	1%	3.0%	4.6%		
Metabolism and nutrition Disorders	0.4%	< 1%	< 1%	1.3%	2.5%	0.8%	0
Pregnancy, puerperium, and Perinatal conditions	0.4%						
Surgical and medical procedures	0.4%	0	< 1%				

Table 28 shows that subjects experienced a similar incidence of defecation pattern adverse events whether they usually used one capsule or two capsules of orlistat per dose.

Table 28: Number of defecation pattern adverse events (AE) and the number of capsules of orlistat used per dose

Defecation pattern AE	Total events N (%)	Events by orlistat dose	
		1 capsule/dose	2 capsules/dose
Yes	84 (51.2%)	63 (51.2%)	21 (51.2%)
No	80 (48.8%)	60 (48.8%)	20 (48.8%)
Oily spotting	25 (15.2%)	20 (16.3%)	5 (12.2%)
Fecal urgency	24 (14.6%)	17 (13.8%)	7 (17.1%)
Liquid stools	18 (11.0%)	12 (9.8%)	6 (14.6%)
Fecal incontinence	16 (9.8%)	12 (9.8%)	4 (9.8%)
Fatty/oily stool	15 (9.1%)	13 (10.6%)	2 (4.9%)
Flatus with discharge	14 (8.5%)	10 (8.1%)	4 (9.8%)
Increased defecation	10 (6.1%)	7 (5.7%)	3 (7.3%)
Decreased defecation	10 (6.1%)	6 (4.9%)	4 (9.8%)
Soft stools	9 (5.5%)	8 (6.5%)	1 (2.4%)
Oily evacuation	7 (4.3%)	7 (5.7%)	0

Pearson chi-square statistic (test of general association between number of capsules per dose and any defecation pattern change AEs) = 0.00 with p = 1.000. Pearson correlation coefficient = 0.00 (no linear association).

7.1.5.1 Eliciting adverse events data in the development program

As shown in Table 26, the adverse event profile seen in the actual use trial parallels the adverse event profile from the randomized, placebo-controlled trials conducted during orlistat product development. A wide range of gastrointestinal adverse events predominantly related to changes in defecation pattern are consistently seen with orlistat use at both the 60mg and 120 mg doses without a significant difference in incidence. These adverse events are directly related to the lipase inhibiting action of the orlistat which decreases the absorption of dietary fat which remains in the fecal material. The high fat content of the fecal material results in this assortment of gastrointestinal adverse events. Other non-defecation-related GI adverse events such as nausea and abdominal pain occur with similar incidence among placebo users and orlistat users.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor used MedDRA with modifications made for orlistat-specific adverse events. This is previously described in the study protocol review in section 6 of this review. The categorizations were appropriate and consistency of terms among studies allowed some cross-study comparisons to be done.

7.1.5.3 Incidence of common adverse events

Please refer to Tables 26 and 27 and associated comments.

7.1.5.4 Common adverse event tables

Please see Tables 26 and 27.

7.1.5.5 Identifying common and drug-related adverse events

Please see Table 26.

7.1.5.6 Additional analyses and explorations

Please see Tables 25, 26, 27, and 28.

7.1.6 Less Common Adverse Events

Please see Table 27.

7.1.7 Laboratory Findings

No laboratory testing was done during the actual use trial discussed in this review.

7.1.7.1 Overview of laboratory testing in the development program

During the clinical drug development program, evaluable laboratory tests were obtained in approximately 1800 patients who received 120 mg TID of orlistat for one year and approximately 600 patients who received 120 mg orlistat TID for two years. Some changes in serum and urine parameters were statistically significant, but the incidence of abnormal laboratory values was similar between placebo-treated and orlistat-treated patients. At the time of review for NDA 20-766, none of the changes were considered clinically significant. Fat soluble vitamin testing and results are discussed below.

Hematology and chemistry
The sponsor's integrated summary of safety summarized laboratory findings for the four Phase III clinical trials submitted in support of NDA 21-887. For the complete blood count, no significant differences were found in the incidences of abnormal laboratory values for subjects treated with orlistat and subjects treated with placebo. For serum chemistries, no significant differences were noted among treatment groups except for serum lipids. After six months of treatment, subjects treated with 60 mg orlistat and 120 mg orlistat showed a mean decrease of 3.1% and 4.9% respectively in total cholesterol compared with an increase of 2.1% seen in subjects treated with placebo. For LDL cholesterol, subjects treated with 60 mg of orlistat and 120 mg orlistat for six months experienced decreases of 5.2% and 6.4% respectively in LDL while subjects treated with placebo had a 2.7% increase in LDL. These serum lipid data were from pooled studies submitted to NDA 20-766. Serum lipid results from study NM17247 showed that subjects treated with 60 mg or orlistat for four months had a decrease in total cholesterol of 3.8% and a decrease in LDL of 5.9%. Subjects treated with placebo had a decrease in total cholesterol of 0.1% and a decrease in LDL of 0.5%.

In pre-clinical trials, high doses or orlistat were associated with increased levels of triglycerides. This effect was thought to be related to systemic inhibition of lipoprotein lipase. The sponsor analyzed the triglyceride levels of 25 patients with serum levels of orlistat greater than 3 ng/ml. There was no evidence that the triglyceride levels were significantly increased when measured at the time of venipuncture for plasma orlistat levels.

Fat soluble vitamins

Clinical studies of orlistat use over one to two years suggest that orlistat treatment decreases the absorption of vitamins A, D, E, and beta-carotene, although decreases in vitamin A (plasma retinol) were not statistically different between orlistat and placebo treatment groups. Small but statistically significant decreases occurred in plasma levels of vitamins D, E, and beta-carotene. Forty-four subjects in the orlistat group required vitamin supplementation compared with twelve subjects in the placebo group. Multivitamin supplementation was started is a subject had two consecutive abnormally low serum vitamin levels. Vitamin K levels were assessed through measurements of prothrombin time and did not statistically differ between active and placebo treatment groups, but data from the literature suggest that decreased vitamin K absorption occurs with fat malabsorption.[2] After one year of orlistat treatment, no clinically relevant changes in prothrombin time were seen among subjects treated with 60 mg or 120 mg of orlistat.

The prescription label for orlistat states:

> *Patients should be strongly encouraged to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition, because XENICAL has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene. In addition, the levels of vitamin D and beta-carotene may be low in obese patients compared with non-obese patients. The supplement should be taken once a day at least two hours before or after the administration of XENICAL, such as at bedtime.*

The following two tables are included in the prescription package insert for orlistat.

Table 9 illustrates the percentage of adult patients on XENICAL and placebo who developed a low vitamin level on two or more consecutive visits during 1 and 2 years of therapy in studies in which patients were not previously receiving vitamin supplementation.

Table 9 Incidence of Low Vitamin Values on Two or More Consecutive Visits (Nonsupplemented Adult Patients With Normal Baseline Values - First and Second Year)

	Placebo *	XENICAL *
Vitamin A	1.0%	2.2%
Vitamin D	6.6%	12.0%
Vitamin E	1.0%	5.8%
Beta-carotene	1.7%	6.1%

* Treatment designates placebo plus diet or XENICAL plus diet

Table 10 illustrates the percentage of adolescent patients on XENICAL and placebo who developed a low vitamin level on two or more consecutive visits during the 1-year study.

Table 10 Incidence of Low Vitamin Values on Two or More Consecutive Visits (Pediatric Patients With Normal Baseline Values *)

	Placebo **/*	XENICAL **/*
Vitamin A	0.0%	0.0%
Vitamin D	0.7%	1.4%
Vitamin E	0.0%	0.0%
Beta-carotene	0.8%	1.5%

*All patients were treated with vitamin supplementation throughout the course of the study

**/* Treatment designates placebo plus diet or XENICAL plus diet

The decrease in serum levels of these fat-soluble vitamins is prevented by concomitant use of a multivitamin if taken at least two hours before or after an orlistat dose.
Information from the integrated database for phase III trials, demonstrates that subjects taking 60 mg orlistat had a significantly lower rate of two consecutive vitamin level measurements below the reference normal range compared to subjects taking 120 mg orlistat. However, at both doses, mean levels of vitamins A, D, E, and beta-carotene remained within the reference ranges after six months and one year of treatment.

The sponsor states that an OTC treatment regimen of 60 mg for up to six months provides a *substantial margin of safety* with regard to reduced fat soluble vitamin absorption but that the OTC label will include instruction to take a multivitamin *as a precaution*. The sponsor states that taking a multivitamin is beneficial to all consumers participating in a weight loss program.

Reviewer Comments:

1. *Despite labeling, consumers may continue to use OTC orlistat for longer than the labeled duration of use or may use it for more than one course of treatment. Given that fat soluble vitamin absorption is decreased with orlistat use and that taking a multivitamin may be beneficial to all consumers on a weight loss program, the sponsor should consider co-packaging a multivitamin with this product.*

   If co-packaging does not occur, the sponsor should provide explicit instruction to consumers about when to take the multivitamin and what the multivitamin should contain. A message similar to that in the prescription package insert should be used. The language chosen to convey the message should be tested for consumer comprehension given that less than half of the orlistat users in actual use study NM17285 used a multivitamin correctly. An actual use study component may not be needed if consumers' understanding can be demonstrated.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This section is not applicable to this review as this study did not involve laboratory testing.

7.1.7.3 Standard analyses and explorations of laboratory data

This section is not applicable to this review as this study did not involve laboratory testing.

7.1.7.4 Additional analyses and explorations

This section is not applicable to this review as this study did not involve laboratory testing.

7.1.7.5 Special assessments

This section is not applicable to this review as this study did not involve laboratory testing.

7.1.8 Vital Signs

Vital signs were not measured during this actual use study.

7.1.9 Electrocardiograms (ECGs)

ECGs were not done during this actual use study.

7.1.10 Immunogenicity

Orlistat immunogenicity was not assessed in the actual use study.

7.1.11 Human Carcinogenicity

This reviewer is not aware of any human carcinogenicity concerns suggested from available postmarketing and drug development data for prescription orlistat, 120 mg (Xenical ®).

7.1.12 Special Safety Studies

This application does not include any special safety studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

As with any weight loss product, there is a potential for abuse or misuse among those with eating disorders. No withdrawal phenomena have been seen with orlistat use up to two years.

7.1.14 Human Reproduction and Pregnancy Data

Based on data from NDA 20-766, prescription orlistat is labeled as Pregnancy Category B. There have been no adequate and well-controlled studies in pregnant women, and orlistat is not recommended for use during pregnancy. In addition, weight loss in conjunction with the use of a low-fat diet is not an appropriate indication for pregnant women.

Orlistat should not be taken by nursing mothers, as it is not known if orlistat is secreted into human milk.

7.1.15 Assessment of Effect on Growth

The actual use study did not enroll subjects under the age of 18 years. In the approved supplemental NDA submitted for the indication of obesity management of adolescent patients down to the age of 12 years, the medical officer noted that trial data showed no evidence that orlistat use impacted height, physical exam, or sexual maturation.

7.1.16 Overdose Experience

According to the 2003 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS), there were no reported toxic exposures, overdoses, or deaths associated with the use of orlistat. The sponsor states that more recent published information from TESS could not be obtained.

7.1.17 Postmarketing Experience

The domestic and international postmarketing experience for orlistat will be presented in the medical officer review from the Division of Metabolism and Endocrinologic Products by Julie Golden, M.D.

7.2 Adequacy of Patient Exposure and Safety Assessments

This review only evaluates safety data from the actual use study. For a comprehensive assessment of adequacy of patient exposure, please see the medical officer review from the Division of Metabolism and Endocrinologic Products by Julie Golden, M.D.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

In this review, the primary clinical data source was the actual use study NM17285.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Some safety data from NDA 20-766 was used to help interpret the adverse event data from the actual use study.

7.2.2.1 Other studies

There are no other study data relevant to this review.

7.2.2.2 Postmarketing experience

This material will be covered in the medical officer review from the Division of Metabolism and Endocrinologic Products by Julie Golden, M.D.

7.2.2.3 Literature

This material will be covered in the medical officer review from the Division of Metabolism and Endocrinologic Products by Julie Golden, M.D.

7.2.3 Adequacy of Overall Clinical Experience

This review discusses the adequacy of clinical experience only with regards to the actual use study.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not relevant to this review of an actual use study.

7.2.5 Adequacy of Routine Clinical Testing

Not relevant to this review of an actual use study.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Data from NDA 20-766 demonstrated that systemic exposure to orlistat is minimal. Approximately 3% is absorbed and most is metabolized during the first pass effect. Orlistat has two inactive metabolites. Fecal excretion of the unabsorbed drug is the major route of elimination. The half-life is one to two hours.

When co-administered with orlistat, the absorption of the following drugs and dietary supplements is decreased:

- Cyclosporine
- Beta carotene

- Vitamin A
- Vitamin D
- Vitamin E

Reviewer comment:

1. *A decrease in Vitamin K is suspected in association with fat malabsorption. However, there were no clinically significant changes in prothrombin times during one year of orlistat treatment.*

Drug-drug interaction studies have revealed no interactions between orlistat and: alcohol, atorvastatin, chitosan, digoxin, fluoxetine, glyburide, metformin, nifedipine (ER), oral contraceptives, phentermine, phenytoin, pravastatin, sibutramine, or warfarin.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This material will be covered in the medical officer review from the Division of Metabolism and Endocrinologic Products by Julie Golden, M.D.

7.2.8 Assessment of Quality and Completeness of Data

This material will be covered in the medical officer review from the Division of Metabolism and Endocrinologic Products by Julie Golden, M.D.

7.2.9 Additional Submissions, Including Safety Update

This material will be covered in the medical officer review from the Division of Metabolism and Endocrinologic Products by Julie Golden, M.D.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

A discussion of drug-related gastrointestinal effects may be found in the common adverse events and drug-related adverse events sections of this review.

7.4 General Methodology

Roche Inc. designed and conducted Study NM17285 as a pilot actual use study before the OTC orlistat development program was sold to GlaxoSmithKline Consumer Healthcare. The drug facts label and other labeling used in the study were different from the labeling submitted in the current NDA. In addition, the user population in the actual use study was predominantly Caucasian with at least a high school diploma. Minorities and individuals of low literacy were

underrepresented among orlistat users in the actual use study. The majority of eligible subjects who chose not to purchase orlistat cited cost as the primary reason.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

In this review, safety and efficacy data from the actual use study are compared to data from pivotal trials from NDA 20-766, but there is no pooling of data.

7.4.1.1 Pooled data vs. individual study data

Not relevant to this review.

7.4.1.2 Combining data

Not relevant to this review.

7.4.2 Explorations for Predictive Factors

Common drug-related adverse events are gastrointestinal in nature and directly related to the increased fat content in the fecal material that occurs with inhibition of pancreatic lipase. This effect is not age, gender, or race dependent. This incidence of these adverse events is similar for orlistat doses of 60 mg and 120 mg.

Please see comments in section 7.2.6.

7.4.3 Causality Determination

Please see section 6.1.3 on pages 27 – 28 of this review for an explanation of causality determination for adverse events.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Dose ranging studies were conducted by Roche, Inc. during clinical drug development and submitted to NDA 20-766. This NDA included a complete report on study BM14150, a Phase II dose-ranging trial with the following study treatment arms: placebo, 30 mg orlistat, 60 mg orlistat, 120 mg orlistat, and 240 mg orlistat. Weight loss was not statistically different from placebo at doses less than 60 mg orlistat, and weight loss was not statistically greater with 240 mg of orlistat compared with 120 mg orlistat. The safety profiles of the 60 mg and 120 mg doses were similar, which is consistent with results from the actual use studied reviewed in this document.

8.2 Drug-Drug Interactions

Drug interaction studies were conducted in the original clinical development program for orlistat. The only drug interactions associated with orlistat use are with cyclosporine and warfarin. Cyclosporine should not be taken within two ours of orlistat or a reduction in serum levels of cyclosporine may occur. Coadministration of warfarin and orlistat did not result in any change in the pharmacokinetics or pharmacodynamics of warfarin. As stated in the medical officer review of orlistat safety for NDA 20-766 (by Eric Coleman, M.D.), long term orlistat treatment does not appear to cause frank vitamin K deficiency as assessed with prothrombin time. However, prothrombin time is not a sensitive indicator of vitamin K deficiency and may remain normal with mild to moderate vitamin K deficiencies. Published literature suggests that fat malabsorption is associated with vitamin K deficiency.[2] Therefore, subjects on chronic, stable warfarin doses should be monitored for changes in coagulation parameters when treated with orlistat. Concomitant use of orlistat and amiodarone may decrease serum amiodarone levels by about 25%; however, according to the sponsor, the clinical significance of this change is not known because there is no established correlation between serum levels of amiodarone and clinical efficacy.

Orlistat has not been shown to interact with diabetes medications; however, as weight decreases, diabetics may need dosage reductions in their diabetes medications due to improvements in glycemic control.

The sponsor states that no clinically relevant drug interactions were seen in two studies that looked at the concomitant use of orlistat with the weight lowering agents, sibutramine and phentermine (Zhi 2002, Kaya 2004).

When co-administered with orlistat, absorption of cyclosporine, beta carotene, vitamin A, vitamin D, vitamin E, and vitamin K are decreased. Please see sections 7.1.7.1 and 7.2.6.

8.3 Special Populations

No special populations are identified for the use of this proposed OTC orlistat product.

8.4 Pediatrics

Orlistat 120 mg is indicated in adolescents 12 – 16 years of age in the current approved prescription label. The proposed OTC target population is adults 18 years and older. This reviewer agrees that a learned intermediary is needed to optimize the diagnosis and treatment of overweight and obesity in individuals under the age of 18 years.

8.5 Advisory Committee Meeting

A joint meeting of the Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee is scheduled for January 23, 2006. Relevant outcomes and recommendations from this meeting will be added to this review prior to completion.

8.6 Literature Review

A literature review was not done to accompany review of the actual use study. **8.7**

Postmarketing Risk Management Plan

The sponsor did not provide a postmarketing risk management plan.

8.8 Other Relevant Materials

There are not additional relevant materials to include with the actual use study review. **9**

OVERALL ASSESSMENT

9.1 Conclusions

In the ANPR for OTC weight loss products, the Panel expressed the opinion that *overweight* is a self-diagnosable condition appropriately treated with OTC drugs. Data suggest that the majority of subjects enrolled in the actual use study complied with dosing instructions and lost weight using orlistat and the accompanying behavior support program. The results are confounded by the following factors:

- Actual use study NM1 7285 was not designed as a pivotal actual use study but as a pilot study to evaluate study design and procedures used for data collection.
- The user population of 237 is fairly small and does not accurately represent the target population of consumers who may use the product if it is available over-the-counter. Individuals of low-literacy and non-Caucasian ethnicity were underrepresented in the study population.
- There is a lack of objective and prospective data collection (subject weights, dietary compliance, use of a multivitamin, adverse event recording)
- Reimbursement procedures during the study and certain questions during the telephone interview may have influenced subject behavior during the study.

- The three month actual use study duration is shorter than the six month proposed duration of use and does not assess subject continuation/ discontinuation of use behaviors after either three or six months or orlistat use.

While these shortcomings in study design and data collection make it impossible to convincingly document orlistat use behaviors and weight loss benefit during the actual use study, data from orlistat use in the prescription setting and in controlled clinical trials suggest that the drug is a safe and effective weight loss agent. No new safety signals were detected from adverse event data submitted with the actual use study or the randomized, controlled trials of orlistat use at either the 60 mg or 120 mg doses. Consideration of all of the information available on orlistat use increases this reviewer's comfort level with potential OTC marketing for this drug.

This actual use study was not designed with primary or secondary weight loss efficacy endpoints, but the data collected suggest that most subjects lost weight while using orlistat 60 – 120 mg TID in the over-the-counter setting. Based on self-reported weights among 62 – 92% of orlistat users, the mean weight loss during the three month study period was 4.8 kg. The mean weight loss based on objectively measured weights at the pharmacy in 16 – 33% of users was 3.3 kg. Based on both self-reported weights and measured weights at study day 60 and beyond, 42% and 49% of subjects respectively lost more than 5% of their body weight. For comparison, obese subjects who enrolled in randomized, placebo-controlled studies and used orlistat 60 mg and 120 mg lost an average of 4.26 kg and 4.65 kg respectively with six months of treatment; however, weight loss above and beyond that of the placebo group averaged 2.4 – 2.8 kg. Weights during the randomized, controlled trials were objectively measured by study personnel. In general, individuals with higher baseline body mass indexes (BMI) lost more weight than those with lower baseline BMIs. This is consistent with weight loss findings from controlled clinical trials conducted among individuals with obesity and those conducted among overweight individuals with BMI of 25 – 28 kg/m^2. These weight loss figures are derived from primarily self-reported weight values from patients that were not confirmed. Objective weight measurements after enrollment were done in a small percentage of subjects and no final objective weight measurements were conducted at the end of the study.

From a safety perspective, the primary concern with OTC orlistat use is the potential for fat-soluble vitamin deficiencies, especially with continuous or intermittent chronic use, labeled or off-label. During the actual use study, the percentage of orlistat users who used a multivitamin at least daily and took it correctly increased from 38% at the 14 day follow-up telephone interview to 53% at the 90 day follow-up telephone interview. The increase in MVI compliance may have resulted from the educational effects of the CATI interview questions. Despite the increase in correct MVI use with orlistat, a minimum of 47% of subjects using orlistat were not using a MVI correctly. Results from the label comprehension study suggest that consumers demonstrated poor comprehension of this key label communication even after MVI use instructions were moved from "Other information" in the actual use study label to "Directions" in the product label submitted with this NDA (see Appendices 10.4 and 10.5). It is not known whether subject confusion arose because labeled directions on the multivitamins differ from the directions for use described on the orlistat label(s).

These concerns are compounded by the low rates of correct self-selection and use decisions by actual use study subjects with labeled exclusions. Study subjects with conditional or unconditional labeled exclusions made correct self-selection/de-selection decisions 0 – 50% of the time depending on the particular labeled exclusion. Overall, 60.2% of 465 subjects with labeled exclusions made a correct self-selection decision. Of 247 subjects with conditional labeled exclusions, only 32% made a correct use decision (chose not to use or said they would consult a healthcare professional first). In the actual use study, it is not clear whether the low correct decision rates reflect deficiencies in label comprehension or whether subjects understood the label and made their decisions based on other factors. Results of the label comprehension study (see the review by Susanna Weiss, Ph.D.) suggest that label elements regarding unconditional and conditional exclusions were generally well understood with comprehension levels > 85%. This reviewer again notes that the NDA label was tested in the label comprehension study but was not used in the actual use study, which was conducted at an earlier time.

All weight loss agents raise the concern of misuse or abuse by consumers who are not overweight or have an eating disorder such as anorexia, bulimia, or binge-eating. Among female subjects in the actual use study, 8.9% of the orlistat users were not overweight by BMI criteria, but many of these women perceived themselves to be overweight. This reviewer recognizes reasonable situations where an individual with a normal BMI would choose to use orlistat for a limited period of time to lose a few pounds while remaining within the normal BMI range. Such individuals may feel better or feel they look better at a slightly lower but normal weight. Given the safety profile of orlistat, this may be an appropriate OTC use for this drug. Unfortunately, consumers with eating disorders sometimes misuse OTC drugs such as weight loss agents and laxatives. Orlistat exerts a physiological effect only when fat is present in the diet. Individuals with anorexia generally eat very little and often do not eat foods containing fat. Individuals with bulimia often induce vomiting or use cathartics following a binge. In these individuals, orlistat would inhibit the absorption of about one third of the consumed fat in the diet. The remainder of the nutrients would be absorbed normally. Binge-eaters comprise about two to four percent of the obese population, and 75% of binge-eaters are obese. One published study suggests that orlistat is effective for weight loss in individuals diagnosed with binge eating disorder when combined with behavioral therapy. The primary safety concern in the small portion of consumers with eating disorders may be the same as that for all OTC orlistat users: the risk of fat soluble vitamin deficiencies developing over time with chronic use.

9.2 Recommendation on Regulatory Action

Pending advisory committee meeting.

9.3 Recommendation on Postmarketing Actions

Pending advisory committee meeting.

9.4 Labeling Review

Please see the review by Arlene Solbeck, M.S. from the Division of Nonprescription Regulatory Development.

9.5 Comments to Applicant

Pending advisory committee meeting.

10 APPENDICES

10.1 Scripted CATI telephone interview questions

Scripted questions for follow-up interviews included the following:

- Have you started to use the orlistat yet?
- Do you plan to use the medicine?
- When do you intend to start using the medicine? (A callback was set for this date and the subject was told that a follow-up call would be make to see if they started the medicine)
- Since you were in the pharmacy to enroll in this study, have you spoken with a health care professional? What did you talk to this health care professional about? (Nurse describes what subject and health care professional spoke about). Whom did you speak with (No specific contact information was obtained).
- Since you were in the pharmacy to enroll in this study, have you referred to the information on the label for any reason?
- When you read the label at the pharmacy, were there things you didn't understand or had questions about?
- What things on the label didn't you understand or did you have questions about?
- There were some support materials that came with the orlistat. Have you read or used any of that material since you first got the medicine at the pharmacy?
- There was a web site mentioned on the box the medicine came in. Did you visit the web site?
- On the days you used the medicine,
  - On average, how many capsules did you use per day?
  - How many times a day did you take the orlistat?
  - Typically how many capsules did you take each time?
- Were there times you took fewer capsules? Why did you take fewer capsules on those occasions?
- Were there times when you took more capsules at a time? Why did you take more capsules on those occasions?
- Since you started to use the medicine, have there been periods of time in which you didn't use the medicine? Why did you choose not to use the medicine? How long, on average, were the periods of time in which you did not take the medicine?
- Since enrolling in the study, approximately what percent of days would you say you used the medicine?
- When did you usually take the medicine? You indicated that there were times when you did not take the medicine with meals. Can you tell me why?
- How often do you take the multivitamin? How do you take it in relation to the orlistat? Did you start taking the vitamin before or after you started taking orlistat?
- Do you exercise? Since you enrolled in the study, how many times per week do you exercise? Is this more, about the same, or less than before you enrolled in this study?

About how long do you exercise each time? Is this more, about the same, or less than before you enrolled in the study?

- Are you following any kind of diet? Is this a supervised diet? Who supervises your diet? What kind of diet are you on?
- How successful are you maintaining this diet?
- Since you enrolled in this study, have you had any discomfort or changes in your health status? What was the discomfort or change?
- Since enrolling in the study, have you gone to the hospital for any reason? What was the reason for your hospital visit? Were you admitted as an inpatient? What was the date that you went to the hospital? What was the date that you were released from the hospital?
- Since you first started to use the orlistat, have you started any new medicines? This would include medicine your doctor prescribed, medicine you can buy without a prescription, vitamins, or dietary supplements?
- Have you become pregnant since you enrolled in this study? What is your due date?
- Since you started using the study medicine, have you lost any weight? About how many pounds have you lost?
- How satisfied are you with this medicine? Could you please explain why?
- Are you still using the study medicine? What was the last date you used the medicine? Do you plan to use it again? When do you plan on using it again? (Nurse uses judgment to classify answer as will use again within 3 months of enrollment, after more than 3 months since enrollment, or don't know).

End of Study Questions:

- Would you purchase the product again? Why?
- Do you think this product was effective in helping you to lose weight? How?
- Why do you think it was not effective in helping you lose weight?
- When you enrolled in the study, you indicated that you have _____. Did you talk with a doctor about this condition either before or after using the medication?
- Why didn't you consult with your doctor before using the product?
- What did the doctor say when you talked with him?
- Why didn't you talk with your doctor?
- Many detailed questions about type of diet subject is using and how often subject eats certain kinds of foods.
- Many detailed questions about reading nutritional labels, reducing fat in diet, target calories, understanding how to calculate calorie and fat information
- What type of activity best describes the type of exercise you typically do? Why do you exercise?
- Did you use any of the materials included in the orlistat package or the dietary and lifestyle information? Which ones? How useful were they? How much do you use them?
- Did you visit the website? How useful was it?
- Is there anything else you would like to tell me about your use of the medicine or your participation in the study? What else would you like to tell me?

10.2 Defecation Pattern/Adverse Event Worksheet

Defecation Pattern/Adverse Event Worksheet

1. Symptom: _____		Start Date: _____		2. Symptom: _____		Start Date:_____	
Inconvenient:	❑ Yes	❑ No	Stop Date: _____	Inconvenient:	❑ Yes	❑ No	Stop Date: _____
Most Inconvenient:	❑ Ongoing:	❑ Duration: _____		Most Inconvenient: ❑	Ongoing: ❑	Duration: _____	
3. Symptom: _____		Start Date: _____		4. Symptom: _____		Start Date:_____	
Inconvenient:	❑ Yes	❑ No	Stop Date: _____	Inconvenient:	❑ Yes	❑ No	Stop Date: _____
Most Inconvenient:	❑ Ongoing:	❑ Duration: _____		Most Inconvenient: ❑	Ongoing: ❑	Duration: _____	
5. Symptom: _____		Start Date: _____		6. Symptom: _____		Start Date:_____	
Inconvenient:	❑ Yes	❑ No	Stop Date: _____	Inconvenient:	❑ Yes	❑ No	Stop Date: _____
Most Inconvenient:	❑ Ongoing:	❑ Duration: _____		Most Inconvenient: ❑	Ongoing: ❑	Duration: _____	

Events with Different Start/End Dates:

Each event could be an AE and should be considered separately according to the following guidelines:

- Asterisked items are always AEs.
- Non-asterisked items are only AEs if they are inconvenient.

Events with the Same Start/End Date:

For each start/end date there should only be one AE:

- Asterisked events will always be an AE, but 2 or more asterisked events will be combined into 1 AE.
- A non-asterisked event will only be an AE if it is the most inconvenient one.
- If the subject can't decide which event is the most inconvenient, then all events will be combined into 1 AE.

  Exception:

- There may be 2 AEs if there is a combination of asterisked and non-asterisked events and the non-asterisked event is the most inconvenient of them all (the most inconvenient non-asterisked event will be one AE ng AE.

istat 60mg Pilot Actual Use Study NM17285
sion 1.1 - Reviewed

10.3 Defecation Pattern Terms, Definitions, and Rules

Defecation Pattern Change Term	Definition
*Fecal Incontinence -	Uncontrolled, spontaneous defecation
*Oily Spotting -	Uncontrolled seepage of oil without stool
*Flatus with Discharge -	Flatus with small amounts of stool or oil
*Fecal Urgency -	Urgent, but controlled, need to produce stools
*Oily Evacuation -	Controlled discharge of oil without stool
*Fatty/oily Stool -	Stools mixed with fat or with a separate oily layer
Liquid Stools -	Stools almost all liquid with very few solid parts
Increased Defecation -	Increased frequency of bowel movements
Soft Stools -	Stools mushy and deliquescent (i.e., stools not formed but of rather fluid consistency)
Decreased Defecation -	Decreased frequency of bowel movements
Pellets -	Stools hard and in the shape of small pellets

1. (*) Attributable to the pharmacological action of orlistat and are always considered as adverse events.

When a subject reported an event that fell into one or more of the categories described above, interviewers asked the following questions to help accurately identify and describe the adverse experience.

1. Was the event controlled or uncontrolled?
2. Was it oil alone, stool alone, or oil mixed with stool?
3. Was the discharge of oil or stool with or without flatus?
4. When did the symptoms start and stop?
5. Was it inconvenient?

The following rules for describing adverse changes in defecation patterns were used.

1. Items marked with an asterisk (*) in this dictionary are attributable to the pharmacological action of orlistat and are always considered as adverse events. These items appear in the list in decreasing order of clinical significance.
2. Terms without an asterisk may represent variations in normal defecation patterns and therefore are considered to be adverse events only when described by the patient as inconvenient.
3. Distinct events occurring at different time points should be reported as separate adverse events.
4. Several events occurring at the same time will be reported as followed: The item described by the patient as most inconvenient should be reported as the adverse event;
    A. If the most inconvenient event is not an asterisked item and there is at least one asterisked item occurring at the same time, the most descriptive term will be reported as a separate adverse event. All of the asterisked items and any remaining non-asterisked ones will be reported as a single adverse event;
    B. If no single item can be identified as most inconvenient, then all items should be reported as one single adverse event.
5. Any adverse experience occurring simultaneously but not listed above should be reported as a separate adverse event.

10.4 Drug Facts Label used in Actual Use Study

Drug Facts

Active ingredient (in each capsule)	*Purpose*
Orlistat 60 mg	Weight loss

Use
- to promote weight loss when taken with a reduced calorie diet.

Warning(s)

Allergy alert: Do not use if you are allergic to orlistat or any of the ingredients in this product.

Do not use
- if you are taking cyclosporine (a drug given after organ transplant surgery), warfarin (blood thinning medicine) or prescription medicines for diabetes

Ask a doctor before use if you have any of the following conditions
- problems absorbing food (malabsorption)
- gallbladder problems
- more than 30 pounds to lose
- been given a diet recommended by a doctor
- diabetes, high blood pressure, or high cholesterol/triglyceride levels.

Ask a doctor or pharmacist before use if you are
- taking medicines for high blood pressure or high cholesterol/triglyceride levels. These prescription doses may need to be changed during weight loss.
- taking any other weight loss medications or supplements.

When using this product
- do not exceed recommended dose (see Directions).
- some of the fat in the food you eat will not be absorbed into your body.
- you may experience gastrointestinal changes such as diarrhea-like symptoms, fatty stools, gas with discharge, and increased bowel movements, especially after meals containing more than 30% fat. *These changes are a natural effect of this product stopping some of the fat from being absorbed into your body. They are often temporary and generally subside within the first weeks of taking the product.*
- eating meals that are low in fat and calories will help you lose weight and also may reduce these side effects. *Remember, for best results, you should be on a reduced-calorie diet that contains no more than 30% fat.*
- read the enclosed user's guide for more information on these side effects.

Stop use and ask a doctor if
- you have an allergic reaction to this product.
- you do not have noticeable weight loss after 3 months of product use.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
- Before using this product, please read the enclosed user's guide for complete directions and other important information.
- This product is for mild to moderately (up to 30 pounds) overweight adults 18 years and older.
- Take 1 to 2 capsules (60 mg) with each meal containing fat, up to 3 times a day.
- This product can be used for up to 6 months of continuous use. If you would like to continue use beyond 6 months, please read the enclosed user's guide.

Other information
- This product can reduce the level of vitamins in your body. Therefore, you should take a daily multivitamin 2 hours before or 2 hours after taking this product.
- Store at 15 to 25°C (59 to 77°F). Keep bottle tightly closed.

Inactive ingredients:
FD&C Blue No. 1, gelatin, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium starch glycolate, talc, titanium dioxide

Questions or comments? Call toll free **1-800-XXX-XXX**

10.5 Drug Facts label submitted with NDA 21-887

Drug Facts

Active ingredient (in each sealed capsule) — **Purpose**
Orlistat 60 mg ..... Weight Loss Aid

Use
- promote weight loss in overweight adults when used along with a reduced calorie and low fat diet

Warnings
Do not use
- if you are taking cyclosporine (a drug given after organ transplant)
- if you have been diagnosed with problems absorbing food
- if you are allergic to any of the ingredients in orlistat capsules
- if you are not overweight

Ask a doctor before use if you have
- gallbladder problems or kidney stones

Ask a doctor or pharmacist before use if you are
- taking medicine for diabetes. Your medication dose may need to be adjusted during weight loss.
- taking warfarin (blood thinning medicine)
- taking other weight loss drugs

When using this product
- you should follow a well-balanced diet that is reduced in calories and contains 30% fat or less. Try starting this diet before you begin taking orlistat capsules. See enclosed Companion Guide for information and tips on how to follow a well-balanced diet that is low in calories and fat.
- orlistat capsules work by preventing the absorption of about 25% to 30% of the fat you eat. Instead of turning into calories, the fat passes out of your body.
- as a result of undigested fat passing through the body, you may experience bowel changes. Examples include fat in your stools and loose and more frequent stools, particularly after meals containing more fat than recommended.
- these bowel changes are related to how the product works and usually subside in a few weeks. You can decrease the likelihood of these effects by reducing the fat in your diet.
- you should start to lose weight within the first two weeks. How much weight you lose will depend on how closely you follow the recommended diet and the orlistat program.

If pregnant or breast-feeding, do not use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
- for overweight adults 18 years and older
- before using this product, read the enclosed Companion Guide for complete directions and other important information
- 1 to 2 capsules with each meal containing fat. Start with 1 capsule. After you have gained experience with choosing meals that contain less than 30% fat, you can increase to 2 capsules for maximum weight loss.
- do not exceed 6 capsules daily
- continue daily use for up to 6 months. If you have not reached your weight loss goal by 6 months, talk to your doctor.
- to ensure adequate vitamin absorption, you should take a multivitamin once a day, 2 hours before or after taking orlistat capsules

Other information
- store at 20 – 25°C (68 – 77°F)
- avoid exposure to excessive light, humidity and temperatures over 30°C (86°F)

Inactive ingredients FD&C Blue No. 2, edible ink, gelatin, iron oxide, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium starch glycolate, talc, titanium dioxide

Questions or comments?
call **1-800-123-1234** weekdays (10:00 a.m. - 4:30 p.m. EST)
Llame a este numbero para obtener una copia de la etiqueta del producto en Espanol.

10.6 Table summarizing study design and results for the following randomized, placebo-controlled trials for orlistat: BM14149, BM14150, and NM17247

Studies to be submitted or referenced in support of the Orlistat 60 mg OTC NDA					
Study Protocol	**Study Period/ #subjects**	**BMI kg/m^2**	**Treatment Arms**	**Measured Outcome/Results**	**Additional Information**
BM14150	24 weeks	28 - 43	placebo TID 30 mg TID 60 mg TID 120 mg TID 240 mg TID	weight loss 30 mg not different from placebo (p=0.106) 60 mg, 120 mg, 240 mg showed statistically greater weight loss than placebo (p≤0.002)	Phase II, MC, DB, R, DD, PC, PD 4 week placebo lead-in period with subjects on a nutritionally balanced weight loss diet (600 kcal/day deficit) Clinic visits q 2 weeks for the first 2 months, then monthly. Mean weight loss compared to placebo: 30 mg = 0.95 kg 60 mg = 1.86 kg 120 mg = 2.55 kg 240 mg = 2.81 kg
NM17247	16 weeks 391 subjects 378 ITT 94% female 89% caucasian	25 to <28	placebo TID 60 mg TID	weight loss in subjects Placebo subtracted mean weight change from baseline: -1.15 kg (p<0.001)	R, DB, PC, PD, MC Primary care setting: mildly reduced calorie diet, no dietary counseling, or behavior modification. Additional 14 days of follow-up. Final telephone contact 14 days after the last dose of study medication.

Studies to be submitted or referenced in support of the Orlistat 60 mg OTC NDA					
Study Protocol	**Study Period/ #subjects**	**BMI kg/m^2**	**Treatment Arms**	**Measured Outcome/Results**	**Additional Information**
BM14149	104 weeks 729 subjects 716 ITT "vast majority" female 99% caucasian	28 – 43	placebo TID 60 mg TID 120 mg TID	First year: weight loss with a 600 kcal/day deficit diet. After 24 weeks, caloric intake reduced by another 300 kcal/day. Second year: weight maintenance with a eucaloric diet. Mean weight loss, year 1: placebo 3.7 kg 120 mg 5.2 kg (p = 0.9) Mean percent weight loss from baseline: placebo -3.5% 60mg -5.6% 120mg -6.9% Mean weight loss, year 2: placebo 1.3 kg 60 mg 4.2 kg (p=0.01) 120 mg 5.2 kg (p<0.001)	Phase III, MC, DB, R, PD, DD, PC 4 week placebo lead-in period prior to 104 weeks of treatment. Overall weight management program: reduced calorie diet, dietary counseling, and behavior modification during the first year. Diet consisted of 3 meals/day with 30% fat, 50% carbohydrate, 20% protein, and a maximum of 300 mg/day cholesterol. Second year eucaloric diet: Caloric intake prescribed = estimated total daily energy expenditure (1.3 x BMR) minus 10% kcal/day. All groups lost about 3% of initial body weight during the 4 week placebo lead-in phase. All three treatment groups tended to regain weight during the second year of treatment. Mean levels of vitamins D, E, and β-carotene in the orlistat groups were reduced compared to placebo at weeks 52 and 104. Compared to placebo, orlistat significantly reduced total cholesterol, LDL-C, LDL/HDL ratio, BP, and glucose and attenuated the rise seen in these parameters during the second year of treatment.

11 REFERENCES

1. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th edition 2006. http://online.statref.com

2. Krasinski SD, Russel RM, Furie BC, et al. The prevalence of vitamin K deficiency in chronic gastrointestinal disorders. Am J Clin Nutr. 1985; 41: 639.

3. Mosby's Drug Consult, 15th edition 2005. http://online.statref.com

4. USP DI Drug Information, 25th edition, 2005. http://online.statref.com

5. Xenical. PDR Electronic Library. http://www.thomsonhc.com/pdrel